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DEGENERATION GRANULES AND VACUOLES IN THE FIBROBLASTS OF CHICK EMBRYOS CULTIVATED *IN VITRO*

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INTRODUCTION

The formation of granules and of fluid vacuoles within the fibroblasts of tissue-cultures is of frequent occurrence in plasma and in Locke's solution, with or without the addition of other substances. There are other types of degeneration. This vacuolization of the cytoplasm is one of the more common modes of cell degeneration and death in tissue-cultures. It has, however, received very little consideration, partly because the vacuoles have often been confused with fat drops and partly because investigators have been reaching out in other directions.

Lewis and Lewis ('15) considered somewhat briefly the granules and vacuoles appearing in the cells of cultures, especially the granules which stain with neutral red, Nile blue B extra, and brilliant cresyl blue 2b. In the normal cell the granules were few in number, but were plentiful in cells with many vacuoles. It was also noted that they accumulate about the central body (centrosphere) and are similar to the granules within the vacuoles. No relationship was found between these granules and mitochondria.

The authors also dealt somewhat briefly with the vacuoles found in the cytoplasm, recognizing that they were signs of degeneration of the cytoplasm and that there was a progressive accumulation in some types of degeneration until most of the cytoplasm was used up and only a framework remained. At first it was somewhat difficult to distinguish the vacuoles from the fat globule spaces in fixed and stained preparations, but in the living cells no such difficulty was encountered. Small dancing granules, varying in number from one to many, were seen within the vacuole; sometimes the granules were motionless and adherent to the wall of the vacuole. It was also found that at times they were colored pale green with janus green. With Nile blue B extra and brilliant cresyl blue 2b the contents of the vacuoles stained pink, and the granules blue or purple. Changes in the shape of the vacuoles and the formation of very unstable, thread-like processes extending out from them were also observed. We were unable to trace any relation between mitochondria and vacuoles, although it was often noted that the mitochondria changed from threads and rods to granules and vesicles, parallel with the increase in the

number of granules and vacuoles, and that in extreme vacuolization the mitochondria were lodged in the cytoplasmic framework between the vacuoles.

Maximow ('16) noted in plasma cultures of subcutaneous tissue of the adult rabbit, fixed with Zenker-formol, embedded in celloidin, cut into histological sections, and stained with eosin-azur, that the fibroblasts contain singular granules which stain bright pink—*i. e.*, are slightly acidophilic. At first these are minute and irregularly scattered in the cell body in small groups. The number of granules varies, but increases with the age of the culture. "In old cultures without cell proliferation all fibroblasts are often crowded full, up to the very end of their outgrowth, with large, round, closely packed granules. . . . . Besides the above granules the protoplasma of many fibroblasts of the same preparation contains small and large vacuoles." In some vacuoles a large or small acidophilic granule of the same character was occasionally detected. Maximow states that the impression produced is that the granules dissolve from the outside inward and form the vacuoles, and that the granules become permanent constituents which are transmitted to subsequent cell generations. He further finds that "the whole cell-body and its processes are then crowded full of spherical, occasionally very large, granules, so that but little is seen of the protoplasm itself." He regards this as an adaptation for life outside the organism. The vacuoles usually present are either scattered singly or joined in groups. "In the fibroblasts embedded in the masses of the old fibrin the majority of the large granules are substituted by vacuoles and the structure of the cell-body appears therefore coarsely foamy." These granules and vacuoles found by Maximow in the fixed and stained cultures of the subcutaneous tissue of the adult rabbit correspond to the granules and vacuoles previously described by Lewis and Lewis, and are probably similar to the ones considered more in detail in the present paper.

Maximow concludes, from cultures fixed in Zenker-formol and stained with iron hematoxylin after sectioning, that the above-described acidophilic granules represent the product of the direct transformation of the chondriosomes. He bases this view upon the very distinct pictures secured by the above method. He says: "The black chondrioconts change into round granules—the mitochondria, which increasing in size seem to transform themselves into the acidophilic granules." This theory regarding the derivation of the above-considered granules and vacuoles from mitochondria is probably quite incorrect. The two types of cytoplasmic inclusions have nothing to do with each other. Maximow's conclusions are such as might be expected from the methods employed by him. He introduces the article under consideration by the statement that heretofore tissue-culture has lacked exact, authentic, systematic researches of a histological character, and that "we lack till now precise information concerning their microscopic structure, their correlation, and, above all, their origin from determined, well-known elements of normal tissue." After this introduction he proceeds to show how cultures should be studied. What could be more absurd than to base practically all conclusions upon observations made on tissue-cultures that have not only been cut into sections, but have also been fixed in the same old mixtures that have so often led observers astray in normal tissues. The very thing we are trying not to do in tissue-cultures is what Maximow seeks to introduce with his histological technique. The absurdity of depending almost entirely upon histological technique, section cutting, etc., will, I think, be obvious to most American observers familiar with cultures. The greatest value of the tissue-culture method lies in the fact that it admits of a study of the living cell, and affords an opportunity actually to watch some of the changes which take place therein, both under the usual conditions of the culture and under various experimental conditions through the introduction of known factors, such as vital stains, various chemical substances, drugs, poisons and other alterations of the medium. Maximow gives little or no attention to observations on the living cell, at least as far as one can judge from his article. This is partly due, no doubt, to the fact that living cells are not so easily observed in plasma as in fluid media. I do not wish to undervalue the use of fixed and stained material, especially total mounts (we use them extensively); but the pictures found in fixed and stained material should be interpreted and controlled from extensive observations upon the living cells. The emphasis, in fact, should be laid on the study of the living cells, and this we have constantly done. It is, of course, more easily accomplished when fluid media are used and the culture grows out on the under surface of the cover-slip, than with the use of plasma. The fixed specimens are of great help in the construction of illustrations, and some structures are more clearly revealed than in the living; but unless they are to be seen also in the latter, their existence in the living cell, as seen in the fixed specimen, must always be open to question.

Maximow criticizes our methods very severely: "In view of the imperfection of their methods (the preparations were made by vapors of osmic acid and examined *in toto,* without making sections) their results are of but little importance." In the first place, osmic acid vapor, with the virtues of which Maximow is apparently not familiar, is a most excellent fixative for cultures in fluid media, far better than any of those employed by him—we have tested them all. It may not answer as well for plasma cultures, but with that we are not concerned. In the second place, there is little point in making sections of cells that are already flattened out on the cover-slip, unless one wishes to trace their origin from the old piece; for that purpose we have, of course, occasionally made sections.

Maximow also criticizes, as have others, the use of Locke's solution. We have never claimed that this solution alone contained all the necessary food-stuffs, but with the addition of dextrose and bouillon or egg-yolk the need can be partially met. Just how complete a supply of food can be given in this manner has not yet been determined. Cultures have been kept alive for a month by washing and changing the medium every day or two, and possibly they might be carried on much longer. The cultures in plasma degenerate somewhat more slowly, as a rule, than those in our solutions, but here also

replantation is necessary for long continued growth. Burrows and Neymann ('17) believe that food materials for the growing cells, in both isotonic salt solutions and plasma, come directly from tissue fragments in the explanted piece through disintegration caused by unfavorable environment. We have long thought that some of the food elements might be supplied in this manner. The conditions, of course, are not normal either in plasma or in Locke's solution, but the first fibroblasts that grow out into the media show no abnormal cytologic changes. The conditions in these embryonic chick fibroblasts undoubtedly differ somewhat from those found in the adult mammalian fibroblasts studied by Maximow.

Burrows and Neymann find that the cells *in vitro* "come to rest after a short period and show evidences of deterioration through vacuolization and failure to stain deeply." These authors evidently recognize that vacuolization is a sign of degeneration. We have not found that the process interferes with the staining of the cells unless they are dead before fixation. A cell may be almost completely filled with vacuoles and yet stain brilliantly with iron hematoxylin and a counter stain.

Luna ('17) found small vesicles or vacuoles appearing in the pigment cells of the retina, cultivated *in vitro*, and as their number seemed to increase with a corresponding decrease in the mitochondria, he thought it probable that they were derived from the latter. Vesicles such as he pictures in his Fig. 7 correspond to the mitochondrial vesicles already figured and described by us in degenerating cells (1915). They do not correspond to the degeneration vacuoles described in the present paper.

MATERIAL AND METHODS

Most of the observations were made on small explants from the legs of 6-, 7-, and 8-day chick embryos cultivated in the usual manner in Locke's solution plus 0.5 per cent dextrose. Such cultures show fibroblasts, clasmatocytes, and often ectodermal membranes and muscle-buds. The cultures of this special series usually reached the maximum growth in about 48 hours. Some of them showed more or less degeneration at 72 hours, and at 96 hours most of the cells were completely degenerated and dead.

I wish to emphasize here that the particular series of cultures (several hundred) used for these observations were made by an inexperienced assistant and that the number of cultures showing granular and vacuolar degeneration was far in excess of that shown in any of our other series where such a mode of degeneration is not by any means the rule. Not only did most of the cultures show such degeneration, but the growth was usually below the average and sometimes there was no growth. I have not been able to analyze the factors responsible for this excessive amount of granular and vacuolar degeneration. The process is, however, essentially the same as that observed in other series except that in the latter case the cultures lived longer with normal appearing cells before degeneration began and that this particular type of degeneration was not so common.

The cessation of growth, of mitotic division, and degenerative changes, may depend not so much on the exhaustion of the food supply as upon the accumulation of waste products in the medium. There was very little fluid in the small drops used in these cultures, and it is possible that it did not take very long for the accumulated waste products to exert injurious effects upon the cells.

Mitotic figures were found in some of these cultures, often many in the same culture at the same time. Such dividing cells are found in the 24-, 48-, and 72-hour cultures. On the other hand, some cultures do not contain a single mitotic figure, and these are usually the ones which show degeneration changes, some even as early as the second day. We are still puzzled by the great differences in the vitality of the cultures, due, perhaps, to unknown factors during the manipulations. This is more especially true when the method is used by an inexperienced worker. The rate and extent of growth are often equal to that seen in plasma.

The living fibroblasts were observed over varying lengths of time in cultures of various ages, both with and without the use of vital stains and various other substances. The vital stains most frequently employed were neutral red and janus black No. 2. The combination of these two stains proved the most satisfactory of all. We have, in the past, frequently used the combination of two vital stains, more especially neutral red and janus green. The latter combination has been used also by Coghill ('15) on fresh amphibian material, and by Mrs. Lewis ('17) on certain eggs and embryos. The neutral red is rapidly taken up by the vacuoles and certain granules of the fibroblasts, while the janus black No. 2 stains only the mitochondria a deep blue-black. Neutral red was used in strengths varying from 1-5000 to 1-800,000 in Locke's solution. For most of the observations I use 1-20,000 or 25,000. The janus black No. 2 was usually of the strength of 1 part of janus black No. 2 to 10,000 or 20,000 parts of Locke's solution. Brilliant cresyl blue 2b and methylene blue (Ehrlich rect. or Harmer Lab.) were also used. These stain the same granules and vacuoles that take up the neutral red.

Until recently we continued to use osmic acid vapor as a fixative with excellent results. Lately, however, the osmic acid in the market has not given satisfaction, and we therefore substituted Zenker's solution without the glacial acetic acid (2.5 per cent bichromic acid solution plus 5 per cent corrosive sublimate plus 1 per cent sulphate of sodium). This has given most excellent preparations when followed, as were the osmic acid specimens, with the iron hematoxylin stain. The cover-slip with the attached growth is immersed in the bichromate corrosive sublimate mixture from ½ to 12 hours, washed and carried through the alcohols with a little Lugol's solution. It must be borne in mind that the procedure here used is suitable for cultures grown in Locke's solution and not necessarily for plasma cultures where the clot acts as a buffer through which the fixatives must penetrate. In cultures in Locke's soluiton the naked cells are exposed to the action of the fixative and the process is correspondingly rapid, reducing post-mortem changes to a minimum. Comparatively few

cultures were fixed, as we relied upon living material for our conclusions. With the iron hematoxylin stain it was often impossible to distinguish between small granular mitochondria and the degeneration granules, as both are stained black. The study of the living culture aids in the interpretation of the fixed material and *vice versa*. Some points would undoubtedly have been missed if only one method had been employed.

DEGENERATION GRANULES AND VACUOLES

Degeneration granules may be characterized briefly as follows:

(1) They are rare or non-existent in the more normal, vigorous fibroblasts of the very young cultures.

(2) They vary in size from the ultramicroscopic granules to ones larger than mitochondrial granules.

(3) They increase in number with the age of the culture.

(4) They tend to accumulate about the centriole or centrosphere.

(5) They are often moved about actively (by cytoplasmic currents), usually in paths from the periphery to the centriole or centrosphere, or *vice versa*.

(6) They take the neutral red stain with great avidity, also brilliant cresyl blue 2b and methylene blue (Ehrlich).

(7) They are not stained by janus black No. 2 which stains the mitochondria.

(8) In fixed specimens stained with iron hematoxylin many of these granules are not distinguishable from mitochondria.

(9) They do not arise from the mitochondria.

(10) The degeneration vacuoles develop about them.

(11) They are probably waste products.

(12) They accumulate under certain conditions in degenerating fibroblasts, and hence might be called degeneration granules.

The degeneration vacuoles show the following characteristics:

(1) They are not found in the normal, vigorous fibroblasts of the cultures.

(2) They are first apparent after there has been a considerable accumulation of granules.

(3) They always seem to form about the granules and almost always contain one or more granules.

(4) When first recognizable the vacuoles are small and contain a relatively very large granule.

(5) They vary much in size.

(6) They tend to accumulate about the centriole or centrosphere.

(7) They often move in paths from the periphery to the centriole or centrosphere, or *vice versa*.

(8) They stain avidly with neutral red, but not as deeply as the granules; they also stain with methylene blue and brilliant cresyl blue 2b.

(9) They are not stained by janus black No. 2.

(10) They often change shape in the living cell, all gradations from spheres to long thread-like channels being seen.

(11) They do not arise from the mitochondria.

(12) They are probably waste products.

(13) They accumulate under certain conditions in degenerating fibroblasts until the latter are often crowded full of them, and then as the cell dies they disappear and the dead cell has a moth-eaten appearance.

The granules and vacuoles especially considered here are most readily singled out from other cytoplasmic inclusions by their property of rapidly absorbing the neutral red dye. It is well known that neutral red stains certain granules in various types of cells in other animals, and the fact that they absorb neutral red does not necessarily indicate that the granules are identical in composition; very likely they are not. We do not know whether the union of the dye with the granule is a physical or a chemical one. Such granules, however, probably have certain characters in common.

The determination of the presence of such granules in the normal, living embryo or animal is most easily accomplished in small, more or less transparent forms that live in an aqueous environment. In embryos, such as the chick, it is more difficult to ascertain with certainty if such granules are normal in any particular type of cell, such as the fibroblast. The mere act of isolating the fibroblast by separating it from the organism in teased preparations, in spreads, or in cultures, immediately alters the environment. Changes in the normal metabolic activity probably follow immediately, and the formation of such granules may result from the changed environment through alterations in the normal supply of gases, salts, carbohydrates, protein products or through the inadequate elimination of waste products from the immediate environment of the cell.

For the present, at least, we are uncertain whether such granules actually exist in the fibroblasts under the normal conditions of the embryo. Occasionally one finds here and there, in cultures less than 24 hours old, fibroblasts entirely free from granules that take the neutral red stain. If these granules do exist normally they are probably small and few in number. Such fibroblasts exhibit a marked contrast to those found in many of the older cultures.

GRANULES IN THE YOUNG FIBROBLASTS

The healthy vigorous fibroblasts of the young cultures are free from vacuoles and contain very few scattered granules that stain red with the neutral red. In the ordinary cultures there are usually to be found, at the end of 24 hours—in the fibroblasts that have migrated from the explant, or other fibroblasts that have arisen from these by mitosis—scattered, clear, refractive granules. They vary in number, often quite markedly, in different cultures and also in cells of the same culture. After 24 hours none of the fibroblasts are entirely free from such granules and many of them also contain small vacuoles with relatively large granules.

DISTRIBUTION OF GRANULES IN THE HEALTHY FIBROBLASTS

The comparatively few granules seen in the fibroblasts of the very young cultures are scattered through the cytoplasm without any definite arrangement, so far as I have been able to determine. Those in the body of the cell, however, approach

to within varying distances of the edge of the much flattened cells. Granules are not uncommon in the larger processes, and here sometimes, since they may be nearly as large as the diameter of the process, they come close to the surface. It is not surprising that the granules are irregularly and apparently indiscriminately scattered through the cytoplasm, as under the best conditions they often move about, usually in a path from the periphery to the nucleus, or *vice versa*, and are thus constantly changing position. As we shall see later, in the fibroblasts of older cultures the granules and vacuoles come to have a very definite relation to the centriole, and their paths of movement are between the centriole and the periphery, rather than between the nucleus and the periphery. The position of the centriole is difficult to determine until there has been a considerable accumulation of granules, but I think if it could be located in the younger, healthy fibroblasts we should find that the granules were moving in paths between it and the periphery, rather than between the nucleus and the periphery. Its close proximity to the nucleus makes it appear as though it were the nucleus that was the center for such activity.

Increase in the Number and Size of the Granules and Vacuoles

As the cultures get older there is a gradual increase in the number and size of the granules and vacuoles. In spite of great variations in the rate of accumulation and the ultimate size of the granules and vacuoles in different cultures, an accurate picture can be given of the more usual process found in the majority of cultures that undergo vacuolar degeneration.

As the granules increase in number it soon becomes noticeable that part of them accumulate at one side or at one end of the nucleus. In fixed material and in later stages this accumulation at the side of the nucleus is clearly seen to take place about the centriole or centrosphere. It is rarely possible to recognize in the living cell, during the early stages of the accumulation of the granules, the centriole or centrioles at or near the center of the granular mass. Since, however, it is possible to do so in fixed material, and at later stages also in the living cell, I have not the slightest doubt but that this accumulation of granules at one side or at one end of the nucleus always takes place about the centriole. This is a very interesting and important point. It is the centriole, then, and not the nucleus that is most directly concerned in the accumulation or location of degeneration granules and vacuoles.

The centriole or the apparatus surrounding it is the determining factor that in some manner governs, by its peculiar metabolic activity, the accumulation of the granules and vacuoles about it. I shall speak of an accumulation of granules about the centriole in these earlier stages, even though in the great majority of instances the centriole was not positively recognized in the living material.

As the granules and small vacuoles increase in number, then, they accumulate more and more about the centriole. The mass is denser at the center than at the periphery, and there are always a few granules scattered through the cytoplasm. With the increase in number of the granules the presence of small vacuoles about many of them becomes more apparent. The granules also show more variation in size, in that many of them are larger than before. As the process goes on, the number and size of the vacuoles gradually increase, so that they form an ever-widening halo about the centriole and centrosphere. Most of the granules become enclosed in vacuoles or show more and more distinctly their vacuolar envelope. Vacuolization may continue until the entire cytoplasm is crowded full of vacuoles except for the enlarging centrosphere and a narrow peripheral margin which usually remains more or less clear. The cytoplasm in such highly vacuolized cells is reduced to a thin framework between the vacuoles, and to a clear, well-defined centrosphere about the centriole that is entirely or almost entirely free of granules or vacuoles. Long spindle-shaped fibroblasts, with the nucleus extending nearly the full width of the cell, often have the centriole at one end of the nucleus, and the cytoplasm between the nucleus and that end of the cell may become packed with vacuoles before any appear in the other end of the cell.

The rate of increase in the number of granules and vacuoles varies greatly in different cultures, and also somewhat among the cells of a single culture. There is, however, usually more variation between different cultures than among the cells of the same culture. No two fibroblasts are ever exactly alike, even in the same culture; yet in spite of this dissimilarity among the individual cells there exists enough uniformity to give a peculiar character to each culture. Since the rate of accumulation of the vacuoles and granules varies in different cultures, often quite markedly, one finds occasionally in a 24-hour culture an accumulation of vacuoles and granules as extensive as in the average 48- or even 72-hour culture. On the other hand, it sometimes happens that a 48- or a 72-hour culture presents no greater accumulation of granules than the average 24-hour culture.

There are many other variations in the number, size, inequality of size, etc., of the granules and vacuoles. It is the control and production at will by environmental alterations of such variations that will enable us to analyze more fully the processes that are taking place. It does not seem beyond the realms of possibility that some day we may be able to produce at will any desired variation.

The above conclusions in regard to the increase in the number and size of the vacuoles and granules were not drawn from the continued observations of individual cells over long periods of time, but from shorter observations on thousands of cells in hundreds of cultures. It would probably be possible so to regulate the conditions of observation that one could follow in a single cell this accumulation of granules and vacuoles from the condition found in the healthy fibroblasts, with few scattered granules, to the completely vacuolized cell, and even to the death of the cell.

Often during the observations, through the manipulation of the culture and the application of neutral red and janus black No. 2, the cells were found to live but an hour or so after the observations were begun. Such cells do not exhibit during that hour or two any marked increase in the number of

granules or vacuoles. Their death may ensue at any stage in the granular and vacuolar formation. Death may also take place at any stage in the cultures that are not thus manipulated. Several factors undoubtedly contribute to the death of the cell, and sometimes one and sometimes another may predominate. In the highly vacuolated cells stained with neutral red the final death process is often quite rapid. The behavior of the colored vacuoles is quite striking; one after another, in rapid succession, they suddenly lose their color and flash out of sight. When the process is complete, the cell has a peculiar, clear, unstained, moth-eaten appearance. Changes in the mitochondria and in the nucleus are also to be seen.

SIZE AND SHAPE OF THE GRANULES

The granules vary in size in the same cell. Some are barely visible with the highest powers, even with the neutral red stain; others are of considerable size and may measure one-quarter or one-half the diameter of the nucleolus. The extreme minuteness of some of the granules indicates that other still smaller, ultramicroscopic ones are probably scattered through the cytoplasm. Within certain limits it can be safely stated that the more healthy the cell the fewer and smaller are the granules. The granules undoubtedly increase in size. One cannot actually see this increase, since the process is probably slow and the difficulty of following the same granule through any considerable length of time is too great.

Most of the granules are somewhat angular in outline, suggesting a crystalline formation. There is but a suggestion of this, however, since they are usually irregularly angular. I suppose an irregular angular mass might result from crystallization or from the accumulation of ultramicroscopic particles. Such granules are difficult to distinguish, by their shape alone, in unstained cells, from the small granular mitochondria (when the latter are present). In most healthy cells, however, the mitochondria are in the form of rods and threads which can be easily distinguished from the degeneration granules. In fixed specimens stained with iron hematoxylin it is likewise difficult or impossible to distinguish between granular mitochondria and degeneration granules. There is a method, however, by which the two types of granules can be distinguished in the living cell; *i. e.*, the combination of neutral red and janus black No. 2, by which the granules are stained bright red and the mitochondria blue-black. Some of the special mitochondrial stains also enable one to distinguish the two types of granules in the fixed specimens; on the other hand, certain fixatives, especially those containing acetic acid, destroy the mitochondria, but leave the granules unaffected.

Maximow noted that the granules described by him were at first minute and irregularly scattered in the cytoplasm. This extreme minuteness of some of the granules is an important point, especially in relation to their possible origin from mitochondria, as alleged by some authors; for it would be logical to assume, if they do arise from mitochondria, that the latter first become reduced in size to a minuteness which renders them invisible, and that this is followed by a change in constitution and a gradual increase in size. Mitochondria are sometimes minute to the limits of visibility and yet retain the characteristic staining reaction with janus black No. 2. The most minute degeneration granules, on the other hand, exhibit the same characteristic coloring with neutral red seen in the larger granules. It is perhaps important to note in this connection that those minute mitochondria are not always or usually found in fibroblasts that are just beginning to show the minute neutral red granules. It is only in the later stages of degeneration that the normal mitochondrial threads and rods tend to break up into granules.

THE RELATION OF GRANULE AND VACUOLE

It is not always possible to distinguish the granule from the small vacuole, as the granule may occupy practically all of the vacuole with only a thin rim of fluid. It may be that all the granules we are considering are included in vacuoles. The fact that granules are often irregular in outline would not nullify such a contention, since vacuoles themselves are sometimes irregular. It is conceivable that even the smallest granule may be surrounded by a rim of fluid too thin for detection. In our present state of knowledge concerning these bodies it is of no particular consequence whether all granules lie within vacuoles or all vacuoles contain granules. Practically all vacuoles do contain granules, one or several, and it is uncertain whether vacuoles exist that are entirely free from granules. We do not know why the vacuole should develop around the granule. It may be that minute vacuoles appear first and granules develop within them, or the granule may appear first and the vacuole develop about it. Since we are not certain of the exact relations when the granules have attained visible size, the ultramicroscopic condition must necessarily be still more uncertain. The impression one gets from the study of numerous specimens is that many of the granules in the healthy cell are free from vacuoles, and that the latter subsequently develop about them. The granules in the smaller vacuoles often appear to be larger than those in the large ones. The larger vacuoles, however, usually contain several granules, with perhaps an aggregate of material equal to the larger granules of the smaller vacuoles.

In vacuoles of the same diameter containing solitary granules, the latter often vary in size. The amount of fluid in the larger vacuoles is much greater in proportion to the size of the granules than that in the smaller vacuoles.

Multiple granules within vacuoles can be conceived of as arising in at least four ways: (1) By the coalescence of smaller vacuoles each with a single granule, the number of granules in the larger vacuole depending upon the number of smaller vacuoles which coalesce; (2) large granules may split up into small granules; (3) new granules may develop in vacuoles, by a process of crystallization, for example; (4) granules free in the cytoplasm might be taken into the vacuole as it enlarges.

THE POSITION OF ORIGIN OF THE GRANULES AND VACUOLES

We have not been able to determine the position of origin of the granules and vacuoles. In the early stages they are

scattered, but as they become more numerous, most of them are located in the immediate region of the centriole. Since they move about freely in the cytoplasm, either towards the centriole or away from it, one might conclude that they form in the more peripheral regions of the cytoplasm and are carried towards the centriole where they tend to accumulate, or that they arise near the centriole and are carried outwards into the more peripheral regions of the cytoplasm. The difficulties of the problem are increased by the fact that the smallest granules are on the boundary of visibility, and from that one must conclude that they begin their existence in the cells as dust-like granules invisible even with the highest powers. Such granules in cytoplasm would be unlikely to be found in their position of origin when they attain the size of visibility. The fact that they accumulate about the centriole may indicate only that they are carried there, as they form, by cytoplasmic currents, if such currents exist; and that these currents tend, during degeneration, to flow more towards the centriole than away from it. Such a view receives some support from the changes which occur about the centriole. We have noted elsewhere that the centrosome increases in size during degeneration, and that about it a centrosphere develops which gradually increases in size until it may become as large as the nucleus. The enlarging centrosphere is usually free or nearly free from granules and vacuoles, the latter surrounding it in a zone of varying thickness.

In cells with many vacuoles and a large centrosphere, the latter is sometimes filled with enormous numbers of the finest, dust-like granules which stain red with neutral red. What relation these bear to the granules under discussion is not known, but very likely they represent a similar degeneration product. We have seen that the ordinary degeneration granules begin to form before the centrosphere appears; thus they may arise independently of it.

THE MOVEMENTS OF THE GRANULES AND VACUOLES

The granules and vacuoles exhibit a considerable amount of movement, different from and more extended than the ordinary mitochondrial movements. It is irregular, sometimes rapid and jerky, sometimes slow and of varying speed. The distances traveled differ greatly; in general, the direction is from the region of the centriole or centrosphere to the periphery, or *vice versa*. The amount of activity varies in different cultures and in cells of the same culture, and is apparently easily affected by environmental factors. Under certain conditions no movements of the granules are to be seen. These movements are probably not dependent upon the activity of the granules themselves, but upon either cytoplasmic currents in which the passive granules are carried or metabolic changes. It has not been possible to see cytoplasmic currents.

As stated above, the movements of the granules are somewhat different in character from the mitochondrial movements; the amplitude is often greater and they are more lively. The movements are best followed in cells where the granules are stained red with neutral red and the mitochondria blue with janus black No. 2. A red granule is sometimes seen passing along close to a blue-black mitochondrium, sometimes extending beyond the extremity of the mitochondrium. Again the granules may pass back and forth in paths that are some little distance from a mitochondrium, and may cross at varying angles above or below a mitochondrium. Sometimes granules are deflected by the mitochondria as the latter are bent, or appear to be bent, by the flowing granules. These appearances are such as to suggest that the granules are located in a more fluid, streaming part of the cytoplasm, while the mitochondria are in a less fluid part, the movements of which would be of a different character, thus giving to the mitochondrium and to the granule each its own peculiar type of motion. On the other hand, the different types of motion may be due entirely to the differences in composition of the mitochondria and of the granules, with a resulting difference in the inter-action between them and the enclosing cytoplasm.

CHANGES IN THE FORM OF THE VACUOLES

The vacuoles vary not only in size and position, but also in shape. In some cells they are constantly altering their form such changes often occurring coincidently with change of position. Frequently many or almost every cell in a culture will show vacuoles that are constantly changing both form and position. Again, very few if any of the cells will show such changes.

The variations in shape which the vacuoles may assume are quite remarkable. The usual form is spherical. This is the most stable condition and such vacuoles may remain unchanged for a long time. In contrast to this may be found a complicated, thread-like network of channels, very unstable and constantly changing. Between these two extremes a multiplicity of forms occur in different cells. The most common change is the sending outward from a vacuole of a long thread-like channel or process. This apparently contains fluid similar to that within the vacuole. These processes are likewise constantly changing their position and length. The entire vacuole may be converted into such a channel, which in rare instances may branch and anastomose with other similar channels to form a more or less complex network with granules scattered here and there within the channels. In such specimens the granules frequently are larger than the diameter of the channel and produce a distinct bulge in its wall. The granules are often observed to shift along the channel.

These vacuolar channels are very unstable and change much more rapidly than the mitochondria. Many of them are about the same size and shape as the mitochondria, and at first may prove to be somewhat confusing; but with the use of neutral red and other vital dyes (methylene blue and brilliant cresyl blue) they can be sharply and clearly separated from the mitochondria. Their behavior, too, is so different that one soon comes to recognize that they are entirely different. The vacuolar channels may change back into spherical or oval vacuoles.

I should suppose that these various changes in the form, and perhaps also in the position of the vacuoles, are dependent upon the metabolic activities, or upon the interchange of substances between the exterior and interior of the cell. The long processes and networks also suggest that there may be some relationship between vacuoles and the canalicular apparatus found in some other types of cells.

MITOCHONDRIA AND MITOCHONDRIAL VESICLES

In the vigorous, healthy fibroblast the mitochondria are usually scattered throughout the cell as long threads or rods, often branching or anastomosing and running in lines more or less parallel to the long axis of the cell; in others, radiating somewhat from the nucleus and centriole towards the periphery. As the granules and vacuoles increase in number the radial arrangement of the mitochondria about the centriole becomes more and more marked. In the earlier stages the mitochondria extend beyond the granular and vacuolar area into the clear cytoplasm. In some of the cultures the mitochondria come to lie in the cytoplasmic net between the vacuoles, and also partly in the clear peripheral regions at the ends of the cells. In such cells, even though the entire cytoplasm becomes packed with vacuoles and granules, the mitochondria may remain as short threads or rods until the cell is about to die.

Other cultures show fibroblasts in which the mitochondria undergo much more change. As the vacuoles and granules increase in number the mitochondria show more of a tendency to break up into short rods and granules, and these in turn may swell up into spherical bodies or vesicles of various sizes. The granules form very minute vesicles and the longer rods may form vesicles as large as the neutral red vacuoles.

These changes apparently begin first in the mitochondria lying immediately about the centrosphere and gradually extend toward the periphery. They are usually preceded by changes in the mitochondria which give them an irregular appearance, and the longer threads seem to be broken up into short rods. The irregularities of the mitochondria gradually become more marked and are chiefly characterized by differences in the diameters of the various threads and of the different parts of the same thread or rod. These changes are also accompanied by irregularities in the staining; that is, the mitochondria exhibit lighter and darker areas, especially with such stains as janus black No. 2. Under ordinary conditions of the culture, these changes in the mitochondria indicate degenerative changes in the cell. Similar changes can be brought about in a relatively short time in the long thread-like mitochondria of healthy fibroblasts by the use of potassium permanganate. With a 1-20,000, 1-40,000, or 1-80,000 solution there takes place with varying degrees of rapidity, depending upon the strength of the solution, changes in the mitochondria similar to those observed in the more slowly degenerating cells of the cultures.

During these changes both the thread and rod-like mitochondria and the mitochondrial vesicles stain bluish with janus black No. 2, and never at any time do they take up the neutral red. In fact, there is always a sharp distinction between the staining of the mitochondria and the mitochondrial vesicles with janus black No. 2 and the staining of the degeneration vacuoles, the granules, and the processes of the vacuoles with neutral red. There are undoubtedly at times certain similarities between the two types of vacuoles when unstained, and in our earlier observations we were uncertain as to the relationship existing. For example, one often sees a small vacuole with a long mitochondrium-like process that is continually changing in shape, size and position. Now both the mitochondria and the neutral red vacuolar processes are subject to constant changes in form, size, and position. As mitochondria form vesicles the vesicular enlargement often takes place first at one end of the mitochondrium; the length of the unchanged narrow portion would vary, of course, with the length of the original mitochondrium and the size of the vesicle at the time of the observation. In unstained living cultures it might be impossible for the untrained eye to distinguish between such a changing mitochondrium and a neutral red vesicle with a mitochondrium-like process. With the application of a 1-10,000 solution of janus black No. 2 the mitochondria and the mitochondrial vesicles are stained bluish, whereas the neutral red vacuoles and granules remain unstained. If this stain is followed by a 1-25,000 solution of brilliant cresyl blue, it will be seen in a few minutes that the color in the mitochondria rapidly disappears, while the previously unstained vacuoles and granules take up the brilliant cresyl blue and appear bluish or violet in color. If, however, the janus black No. 2 is followed by neutral red (1-20,000 or 1-25,000), the blue color of the mitochondria and the mitochondrial vesicles is often increased in depth, while the previously unstained vacuoles and granules take up varying amounts of the neutral red dye. Then, too, the differences in the behavior of the two types of vacuoles when stained and followed with the application of potassium permanganate or chloroform indicate that we are dealing with two quite different things.

In some cells with almost complete vacuolization the mitochondria may show very little sign of degeneration or change, but appear as rods and short threads in the cytoplasmic network between the vacuoles. In some of the long spindle cells vacuolization may be complete at one end of the cell and the mitochondria be more or less broken up into rods and granules; while at the other end, the nucleus lying between the two parts, there may be almost complete absence of vacuoles and granules, and very little change in the long thread-like mitochondria. The degenerating end of such a cell seems to be always the end containing the centriole.

CHANGES IN THE REGION OF THE CENTRIOLE

As the cultures get older there is a gradual increase in the number and size of the granules and vacuoles. Parallel with this increase very important changes take place in the region of the centriole. As the granules increase in number, they tend to accumulate about the centriole, which is located near one side or one end of the nucleus. This gradual accumulation

of the granules, and later of the vacuoles, about the centriole gives a very characteristic picture, especially when the granules and vacuoles are stained with neutral red. One is often unable to recognize the centriole in the earlier stages in the living cell. In fixed material the centriole can usually be seen at the center of the mass of granules and vacuoles. Later, as these accumulate, the centriole becomes surrounded by a more or less clear area (the centrosphere) near the center of the mass of granules and vacuoles, and near one side or one end of the nucleus, with which it is more or less in contact. As the granules increase in number, the centrosphere increases in size, and at its center can usually be detected the double centriole. The centrosphere is usually entirely free from neutral red granules and vacuoles. It gradually increases and may eventually attain a diameter equal to, or even greater than, that of the nucleus. With its enlargement the granules and vacuoles appear to be pushed farther and farther away from the centriole. The centrosphere usually presents a clear medullary zone immediately about the centriole or centrioles, and a much wider cortical zone, which often shows radiations. Occasionally one or two small neutral red granules appear to lie within the centrosphere. In some cultures which have been stained with neutral red the centrosphere shows many very fine, red, dust-like granules. Since this seems to occur only in cells that show somewhat advanced vacuolar degeneration, it may be that it is indicative of the beginning degeneration of the centrosphere.

We have already considered the radial arrangement of the mitochondria about the centriole and centrosphere; the granules and vacuoles, lying between the mitochondria, also at times assume a more or less radial arrangement. We have considered also the movements of the granules and vacuoles which take place more or less in paths between the centriole or centrosphere and the periphery. The accumulation of granules, vacuoles, and mitochondria about the centriole, and the accumulation or building up of an increased amount of what seems to be a special type of cytoplasm about the centriole, would indicate that its activities are in some manner increased during the degeneration of the cells.

DISCUSSION

I venture to suggest that in due course of time it will be found that the living part of the cell cannot be stained by any of the so-called vital dyes, since the combination of the dye with the living protoplasm would so upset the delicate molecular constitution of the latter as to kill it; and because living protoplasm is so constituted that it cannot combine, either physically or chemically, with any other substances except such as are synthetically built up into itself. The corollary will be that the so-called vital dyes stain only the non-living cytoplasmic inclusions, such as granules, vacuoles, secretion granules, food-globules, mitochondria, etc.

One might well hesitate to class the mitochondria with non-living cytoplasmic inclusions, in view of the many claims that have been set forth as to the rôle of mitochondria in the transmission of hereditary qualities, and above all as to their part in the formation of various cell structures during histogenesis. They are supposed to form the collagenic fibers (Meves), myofibrils (Benda, Meves, Duesberg, Hoven and others), epidermal fibers (Firket and Duesberg), neurofibrils (Hoven, Meves and G. Arnold), and secretion granules (Grynfeltt, Bobeau, Regaud and Marvis, Nicolas, Regaud and Favre, Hoven and others)—a formidable list of authors imbued with the idea that the mitochondria possess magic qualities. Cowdry, in his recent excellent contribution, "The Mitochondrial Constituents of Protoplasm," states that "the radical claims concerning their rôle in histogenesis have forced the reinvestigation of the entire field." He is inclined to believe that the mitochondria are concerned, either directly or indirectly, with metabolism or with protoplasmic respiration. The mitochondria may well play an important rôle in the general metabolism of the cell, more especially in that particular part of the metabolism which is common to all cells, such as respiration, perhaps, as has been suggested by several authors (Kingsbury, Mayer, Rathery and Schaeffer). The mitochondria might play such a rôle in the general metabolism of the cell and still not be considered as a part of the living cytoplasm, any more than are the stored-up yolk-granules found in many eggs.

Coghill suggests that during the process of digestion and assimilation of yolk in amphibian embryos certain end-products of the process segregate into what he calls *alpha bodies* and *beta bodies*, and that the former, probably undergoing some chemical change, become free as mitochondria in the process of assimilation into protoplasm. Whether this be true or not, more interesting still is the suggestion that the more toxic action of janus green (which stains the mitochondria), as compared with that of neutral red (which stains the beta bodies), is due to the fact that the processes leading up to the construction of protoplasm are obstructed by the reaction of this stain; whereas, only the residue, so to speak, of these processes is attacked by the neutral red. If the mitochondria are concerned in the respiration of the cell, the action of janus green on the mitochondria, for which it has a special affinity, might obstruct the respiration to such an extent as to kill the cell. Coghill's suggestion as to the less toxic action of neutral red would apply to our conception that neutral red stains only the non-living matter, such as accumulated waste products or stored-up food-stuffs, or some partially digested food-stuffs that are not immediately essential to the cell.

Granules with a special affinity for neutral red have been described in many different types of cell in many different species of animals, and it will be interesting in this connection to consider a few of the more striking cases. Fischel ('01) found in the living ectodermal cells of amphibian larvæ many such granules. He considered them as living elements, in conformity, perhaps, with the views of Altmann prevalent at that time. We know that the ectodermal cells of various vertebrates deposit within themselves substances which are usually considered as non-living elements, and which in many cases ultimately accumulate to such an extent as to finally transform the cell into a non-living scale. The fact that such

deposits may serve a useful purpose in the organism does not invalidate the view that they are non-living inclusions.

The Clarks have described in the lymphatic endothelial cells of the tadpole's tail numerous granules which take up the neutral red in the living. E. R. Clark has shown that the lymphatic endothelium is actively phagocytic, and since these cells possess the power of taking up particulate matter it may well be that they also take in ultra-microscopic particles and segregate them into granules that take up the neutral red. Whether these granules are of this nature, or whether they consist of waste products, is of course impossible to determine at present. Other phagocytic cells, such as the clasmatocytes and leucocytes, are especially rich in vacuoles and granules that have a great affinity for neutral red. The clasmatocytes are especially interesting in this connection, as they are abundant in most of our cultures. Certainly the vacuoles, and probably all the granules which stain so avidly with neutral red, are non-living inclusions, the granules for the most part being derived from cellular debris taken up by the cells.

It is well known that the partially digested dead contents of the food vacuoles of protozoa stain with neutral red (Plato, Stolc) and that disintegrating bacteria and cell debris in leucocytes stain in a similar manner (Plato, Arnold). Many eggs contain numerous granules and globules, probably food-stuffs, and perhaps accumulated waste products also, that stain with neutral red. The eggs of Cerebratulus, of the sand-dollar, and of Lophius piscatorius (M. R. Lewis), as also the amphibian egg (Coghill), have recently been studied with the aid of neutral red, and all were found to contain numerous neutral red-staining granules probably of the nature of stored-up food-stuffs.

There are reasons for believing then that the granules and vacuoles considered here are non-living cytoplasmic inclusions. Since the granules and vacuoles accumulate without noticeable enlargement of the cells, they must be formed in greater part from the cytoplasm rather than by the diffusion into the cell of substances and fluid from the outside; moreover, they are formed from the cytoplasm, presumably as products of the metabolism of the living cell. These products of metabolism may be divided into two classes—food products and waste or secretion products. The former are found most abundantly in egg and embryonic cells, and we should scarcely expect to find cells cultivated in Locke's solution storing up food-stuffs. We are led, therefore, to accept the alternative theory, *i. e.*, that the granules and vacuoles are accumulated waste products and that they are formed in part, at least, by the breaking down of the cytoplasm. This process may be looked upon as a degeneration phenomenon, since it ultimately leads to the death of the cell.

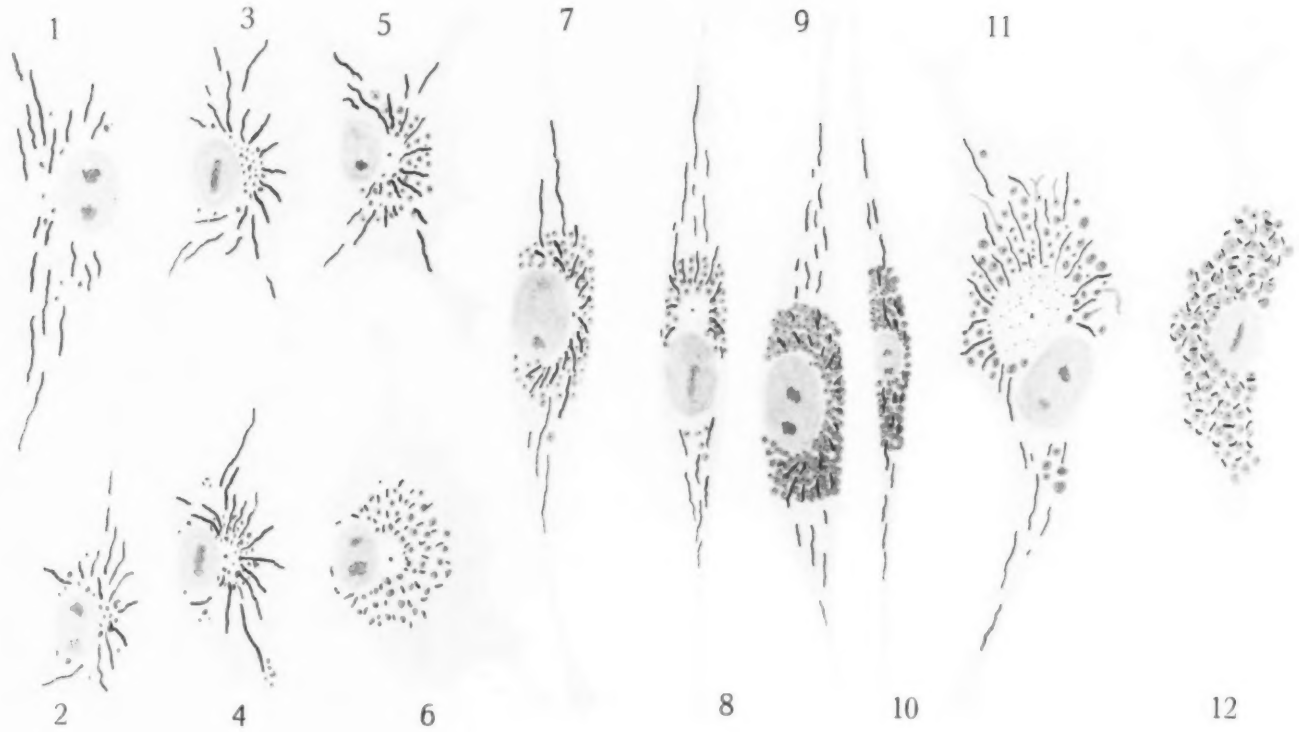
The altered environment of the fibroblasts in the cultures probably sooner or later interferes in many ways with their normal metabolism, either from the absence of oxygen, salts, or food-stuffs, or through the accumulation in the culture medium of waste products in sufficient amount to prevent their normal elimination from the cells by osmosis. This altered environment with its lack of certain essential salts, food-stuffs, and perhaps of oxygen, would favor the breaking down of the cell protoplasm through starvation and the accumulation of waste products. We have no method of determining whether the contents of the vacuoles and granules are identical with the normal waste products excreted from the cell. An alteration in the composition of the waste products, however, might be expected to accompany the starvation of the cell.

Since the cells do not appear to increase in size as vacuolization spreads, we are more or less forced to conclude that part of the cytoplasm is broken down into granules and vacuoles. This process may use up most of the cytoplasm, leaving only a slender framework between the vacuoles. The enlarged centrosphere usually remains intact and does not become vacuolated. The cytoplasmic framework is continuous with the centrosphere, radiating out from it in all directions.

The relationship of the granuoles and vacuoles, and likewise of the mitochondria, to the centriole and to the gradually enlarging centrosphere is not at all clear, if we attempt to explain it in physiological terms. The anatomic picture is plain enough, but why the granules and vacuoles should surround the centriole and centrosphere is unknown.

The centriole and its centrosphere have long been considered by many authors as the dynamic center of the cell, the focal point of the more active archoplasm of Boveri, the kinoplasm of Strasburger, the spongioplasm of Leydig, etc. This peculiar cytoplasm, which accumulates about the centriole during degeneration and which I have also seen much augmented in amount in giant cells in certain cultures, seems to be different from the ordinary cytoplasm that occupies the bulk of the cell. Whether there is an actual increase in the amount of the stuff forming the centrosphere or merely a concentration of already existing material about the centriole, is difficult to determine. There appears, however, to be an actual increase.

Conklin speaks of the spongioplasm of the egg of Crepidula as "the interalveolar or continuous substance within which are found enchylemma, microsomes, mitochondria, as well as yolk, oil, and other inclusions." He finds that "large inclusions such as yolk spheres are forced out of regions where the spongioplasm concentrates." A somewhat similar phenomenon seems to take place about the enlarging centrosphere, where the vacuoles and granules are forced away by the concentration or increase in the archoplasm or spongioplasm about the centriole in the degenerating fibroblasts. The framework of cytoplasm, which extends from the centrosphere to the peripheral layer in these highly vacuolized fibroblasts, corresponds, perhaps, to the spongioplasmic framework in Crepidula that remains throughout the entire cell and connects the nucleus and centrosphere of the resting stages to the peripheral layer after the centrifugal force has displaced the more fluid part of the cytoplasm, the yolk, and the other cytoplasmic inclusions. It is the spongioplasm that seems to be the living part of the cytoplasm, the part which determines the polarity of the cell. In the normal fibroblast the cytoplasm, except for the mitochondria and a few granules, appears homogeneous. Does this apparent homogeneous cytoplasm consist of two parts,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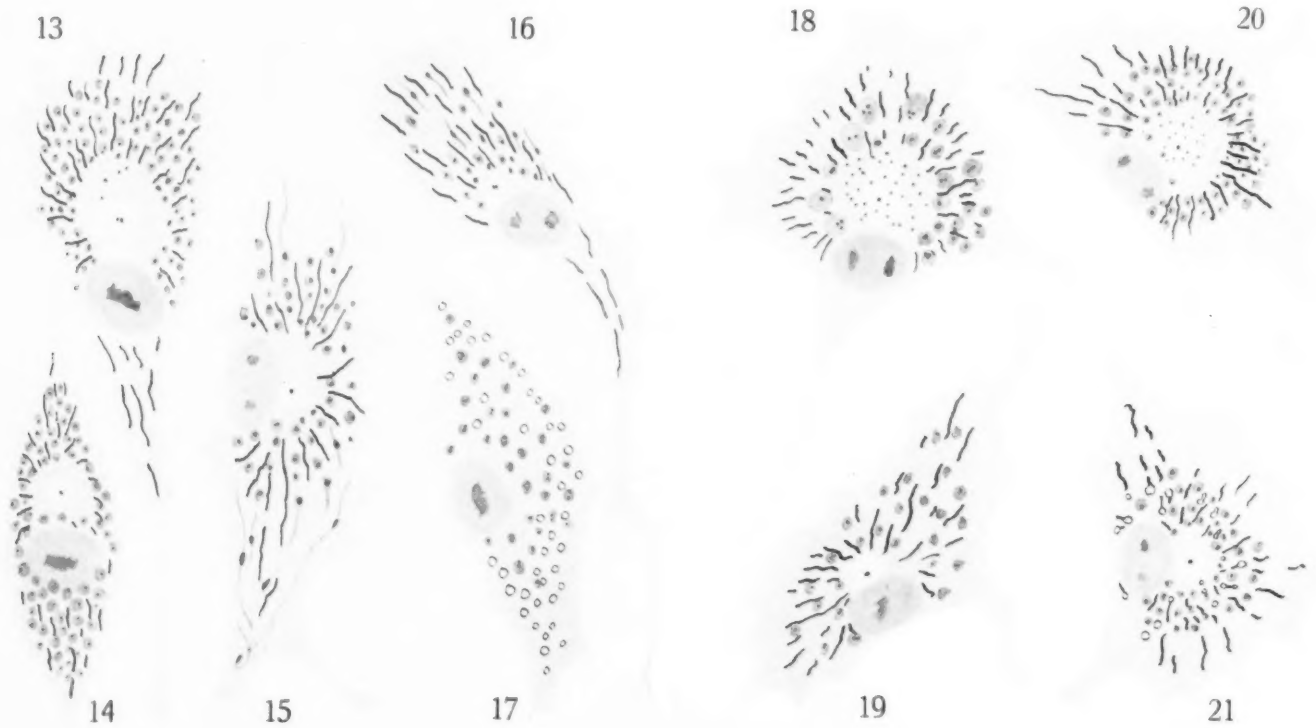
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a spongioplasmic framework and a more fluid enchylemma? Or is it all spongioplasmic material, except for the inclusions above noted?

The causes of, or factors concerned in, the gradual enlargement of the centrosphere are not known. It is well recognized that in many eggs where food accumulations are considerable the attraction sphere is large. It is also larger in cells that are about ready to divide than in the resting cell. There is undoubtedly a relationship between the accumulation of foodstuffs in the egg and the size of the attraction sphere; and again, between the growth in size of cells which are destined to divide and the increase in the size of the attraction sphere.

Is the accumulation of granules and vacuoles about the centriole the factor that causes the enlargement of the centrosphere? Such an accumulation of granules and vacuoles would naturally alter the usual relationship of the centriole to the periphery of the cell, upsetting the metabolic balance in such a manner as to cause, perhaps, the building up of the enlarged centrosphere, since the metabolic activities which are centered in the centriole probably depend upon a constant interchange of materials between the centriole and periphery. The accumulating waste products about the centriole in the form of granules and vacuoles would certainly tend to alter this.

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EXPLANATION OF FIGURES

The figures are all drawn free hand from living cells stained with neutral red, and many of them with janus black No. 2 in addition. The original drawings gave only vague outlines for the cells, as the author's attention was concentrated on the relations of granules, vacuoles, mitochondria, centriole, centrosphere, and nucleus. Since then the borders of similar cells, both in living and fixed material, have been examined, and appropriate outlines added to the original cell drawings. Thus the greater number of the figures are composites. The edges of most of the fibroblasts present a peculiar scalloped condition, with slender processes of varying lengths extending from the points, much longer, as a rule, than those shown in the figures.

Figs. 1, 2, 3, 4, and 5 are from 78-hour-old cultures; explants from the legs of 8-day chick embryos. Figs. 2 and 3 are from the same culture, the others are each from a different culture.

Fig. 1.—Healthy fibroblast with few granules. Figs. 2, 3, 4, and 5 show the gradual accumulation of granules about the centriole and the increasing radial arrangement of the mitochondria. In Fig. 5 are also seen many small vacuoles. Fig. 4 and 5 show small centrospheres.

Fig. 6.—A 74-hour-old culture; explant from leg of 9-day chick, showing increased number of vacuoles and granules about an enlarged centrosphere. Mitochondria broken up into short rods.

Figs. 7 and 8.—54-hour-old cultures; explants from leg of 8-day chick. In Fig. 7 the centrosphere is at the side of the nucleus and the granules, vacuoles and mitochondria are arranged more or less symmetrically and radially about it. In Fig. 8 the centrosphere is at one end of the nucleus. Very few granules or vacuoles are seen in the opposite end of the cell.

Figs. 9 and 10.—78-hour-old cultures; explants from leg of 8-day chick. The centrosphere either has not developed or is obscured by the crowded granules and vacuoles. The centriole was not seen, but its position in both cells is undoubtedly at the side of the nucleus.

Fig. 11.—A 78-hour-old culture; explant from leg of 8-day chick. Large centrosphere surrounded by granules, vacuoles, and mitochondria. Wide cortical zone of centrosphere shows radiations. The vacuoles in this cell were constantly sending out long processes.

Fig. 12.—A 48-hour-old culture; explant from the leg of a 7-day chick. Cell crowded full of large vacuoles, except at the thin edge. Mitochondria broken up into short rods which seem to lie in the cytoplasmic framework—centrosphere obscure.

Fig. 13.—A 48-hour-old culture; explant from leg of 7-day chick. Very large centrosphere surrounded by many large vacuoles. Radially arranged mitochondria, rather long rods and threads. No vacuoles or granules in the opposite end of the cell.

Fig. 14.—A 2-day-old culture; explant from leg of 7-day chick. Large centrosphere; entire cell crowded with large vacuoles; mitochondria in form of short rods.

Fig. 15.—A 3-day-old culture; explant from leg of 7-day chick. The vacuoles showed much motion and were constantly sending out long processes or changing into channels, which are seen to anastomose at one end of the cell.

Fig. 16.—A 24-hour-old culture from the leg of a 7-day chick. The vacuoles and granules showed considerable motion, and the vacuoles were constantly sending out processes and changing in form.

Fig. 17.—A 3-day-old culture from intestine of a 7-day chick. The mitochondria have all changed into vesicles. Degeneration has progressed to such an extent that the vacuoles have begun to disappear.

Figs. 18, 19, and 20.—2-day-old cultures; explants from the legs of 7- and 8-day chicks; showing variations in the vacuoles, centrosphere, etc. Centrosphere full of dust-like granules.

Fig. 21.—A 3-day-old culture; explant from leg of 9-day chick. Mitochondria are changing into vesicles.

SOME ASPECTS OF OVARIAN PREGNANCY. WITH REPORT OF A CASE

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Although the first case of ovarian pregnancy under that heading in the *Index Medicus* is that of Kouwer ('97) (van Tussenbroek, '99), careful scrutiny of the titles listed for the last decade reveals the fact that 5 cases of ovarian pregnancy were reported in 1908, 4 each in 1909 and 1910, 7 in 1911, 13 in 1912, 9 in 1913, 7 in 1914, 3 in 1915, 1 in 1916, and 5 in 1917. This makes a total of 58 cases apparently reported within this decade. Since the reports on some of the cases were published in three different journals, these were, of course, counted merely as one, and although the authenticity of four of the cases must be questioned on the basis of the titles alone, the series, nevertheless, is a large one in spite of these facts and of a marked decline in the number reported during the war. Since Norris ('09) stated that only 19 certain cases, approximately only one-third as many as all cases listed in the last decade, were reported in the decade between 1899 and 1909, it would seem that ovarian pregnancy not only is receiving increasing attention, but that a change in attitude probably is in progress. This conclusion would seem to be justified even though a careful examination of the descriptions of the cases reported in the decade between 1908 and 1917 would reduce somewhat the number listed.

Lockyer ('17) accepted as authentic only 22 cases of those reported between 1910 and 1917, but his review is only a partial one. Even so, it shows that there is a decided increase in the number of cases which have been regarded as genuine from decade to decade. The marked increase in the number of genuine cases reported in recent decades becomes still more evident if one recalls that Williams ('10) found only 13 positive cases up to 1906, whereas Norris found 19 positive cases in the single decade between 1899 and 1909. That is, Norris found more positive cases reported in this decade than had been reported in all previous medical history up to 1906. This surely is a significant fact.

The opinion that many, even if not all, cases of so-called hematocele, hematoma, apoplexy, blood cysts, and rupture of the ovaries, probably are nothing but cases of ovarian pregnancy in disguise, has been held by various investigators for some time. Hence, if hematocele of the ovaries repeats the history of hematosalpinx, it is not unlikely that the near future will see a marked increase in the reported frequency of "a fact so curious and important in itself," as Granville aptly put it a century ago. This would seem to be true in spite of the fact reported by Norris and Mitchell ('08), that only a single case of ovarian pregnancy was found among 44 extra-uterine specimens and 58 hemorrhagic cysts contained in the collection of 1700 gynecological specimens at the hospital of the University of Pennsylvania. At any rate, a careful microscopic examination of all such cases would seem to be indicated in the future in order to determine, if possible, which cases are, and which are not, conceptual in origin.

To-day it is no longer true, as stated by Freund and Thome ('06) and by Sencert and Arom as late as 1914, that authentic cases of ovarian pregnancy belong to the great rarities. Yet the fact that many of our states, as well as many large clinics, have not a single case on their records seems to suggest that the condition still is seldom recognized, a century after Granville observed his first case. Moreover, a number of continental gynecologists and obstetricians, for a quarter of a century, have regarded the occurrence of ovarian pregnancy as undoubted. Anderson ('17) stated that German writers began to report cases of ovarian pregnancy with some frequency after 1901, and Gilford ('01) also called attention to the fact that continental opinion long had accepted ovarian implantation not only as possible, but as proven. Gilford further referred to the often quoted opinion of Tait that ovarian pregnancy is as rare as "A blue lion or a swan with two necks," and in his article in 1899 also called attention to the opinion of Bland-Sutton, that ovarian pregnancy not only has no existence, but that it is impossible. These opinions are particularly interesting in view of the careful reports made by Granville (1820 and 1834), in connection with the two cases which he then and which others since have regarded as cases of undoubted ovarian pregnancy, in spite of the absence of microscopic examination. In view of this lack it is particularly fortunate that both of these reports of Granville are accompanied by splendid illustrations by Bauer, which also won his praise and admiration and which greatly strengthened his cases. It may be recalled in this connection that Werth ('01) accepted Granville's case recorded in 1820, but said nothing about his second more convincing instance reported in 1834.

Although there is as yet no agreement as to what constitutes an authentic case, a review of the literature justifies the growing and apparently well-founded belief that in the past too much emphasis has been laid on certain criteria which later experience has shown to be partly inapplicable. It is becoming clear that some cases, formerly excluded for reasons regarded as sufficient, with our present knowledge could no longer be rejected. Moreover, it does not seem at all improbable that some cases listed as *tubal* really were *ovarian* in origin. Nor must it be forgotten that not even the entire absence of remnants of the conceptus can positively exclude a case from the category of true ovarian pregnancy. In a number of cases in the literature, and also in the present case, the clinical history and gross anatomic findings suggest the conclusion drawn by Scott ('01) on *a priori* grounds alone, that the conceptus may be completely resorbed. It may, of course, also be aborted and disintegrate completely. That such an

assumption is justified is indicated by the lysis of the embryo or fetus in a large number of cases of ovarian pregnancy, and also by the very degenerated condition of some of the vesicles and of the surrounding ovarian stroma. The possibility of such an occurrence is established also by similar events in the uterine and tubal pregnancies discussed elsewhere (Meyer, '19), and probably is illustrated by such cases as those of Anning and Littlewood ('01), in which no mention is made of an embryonic disc in a translucent conceptus the size of a "pea." Then, to be sure, there are the cases of unruptured ovarian pregnancies containing villi only, as well as the rare case, probably of double ovarian pregnancy, of Holland ('11). Although one cannot be certain that embryonic tissue was removed from the left ovary with the blood-clot which was forcibly expelled at the time of operation, it is not at all improbable that the small plasmodial masses found in the left ovary were the only remnants of the conceptus. I realize fully that the conclusion that young conceptuses may be wholly dissolved is fraught with great uncertainty, but I am quite sure that it is justified by the facts, and that it therefore is in the direction of truth. It could only fail to be so if every ovum that becomes implanted within the ovaries were aborted or were removed by operation before lysis was possible.

One cannot rightly refuse to recognize the possibility of the spontaneous disappearance of an ovarian pregnancy. Since implantation in the ovary occurs under such abnormal conditions, it would seem that for this reason alone the great majority of such implantations inevitably must succumb. This would seem probable wholly aside from considerations regarding the development of the corpus luteum, although lack of, or interference with, the development of the latter also would seem to condition early death of the conceptus if the results of the long series of experiments on rabbits by Frankel ('03-'10) are indicative of the rôle played by the corpus luteum in early implantations in man also. It surely is difficult, if not impossible, to see how implantation within the Graafian follicle, and especially the later development of the conceptus, can fail to interfere with the development of a normal corpus luteum. Cases in the literature, and also in the present case, did not reveal the presence of any well-preserved or even true luteal cells at the time the pregnancy was terminated. Although this fact does not presuppose an entire lack of development of these cells in the earliest stages of the implantations, it undoubtedly does imply a defective development, which in itself may have become responsible for the death of the conceptus. Nor should the possible toxic effect upon the conceptus of luteal cells be forgotten in this connection.

I do not assume, to be sure, that the clinical symptoms and signs alone should suffice finally to group a specimen as truly ovarian, but when these are indicative of the presence of an ectopic gestation, and when undoubted intra-uterine decidual changes are present, in the absence of abdominal pregnancy or tubal involvement and a normal corpus luteum, and the presence of a blood-clot within the ovary, there would seem to be little reason for doubting the authenticity of the ovarian implantation even in the absence of embryonic remnants. Since changes suggesting decidual reaction in the ovary have been reported so seldom it is doubtful whether much emphasis can be laid on them. One seems justified in saying this in spite of the fact that the presence of decidua in the ovary formed the only anatomic evidence upon which Kantorowicz ('04) confidently classed his two rather advanced cases of ectopic pregnancy among the authentic. Moreover, if it be true, as stated by Webster ('04) that changes which cannot be distinguished from true decidual changes not infrequently occur in the ovary in connection with normal uterine pregnancies, then the presence of islands of decidual cells in an ovary surely cannot be regarded as indicative of ovarian pregnancy. I wonder, however, whether it would not be possible to distinguish genuine decidual cells by modern histochemical methods. In making this observation, I am fully aware that various criteria have been advanced from time to time by means of which to judge ovarian pregnancies, and that many of these have met with objection and have hence been modified. Such modifications would seem to be inevitable as long as there is progress in the solution of an unsettled question.

The absence of the fetus in many of the recorded cases in itself demonstrates the entire inapplicability of the criterion added by Jacobson ('08). Moreover, the histologic appearance of the ovarian tissue around certain portions of the blood-clot in the present, and also in some of the cases in the literature, would seem to suggest that it may be very difficult to find remnants of ovarian tissue at several points in a case of pregnancy which has advanced far. Hence, this criterion of Spiegelberg ('78) cannot be regarded as necessarily crucial. Whenever the implantation is developed at the outer instead of at the inner margin of a follicle, as in the case of Banks ('12), early destruction, even if not early rupture, of the overlying ovarian stroma and capsule would seem to be inevitable. Indeed, whenever the layer of ovarian stroma overlying the placenta is thin, very early death of the fetus would seem to be inevitable from defective nutrition alone. On the other hand, when placental development occurs in the region of the follicle directed toward the body of the ovary, great destruction of the ovarian stroma would seem to be unavoidable, even if something akin to normal decidual formation actually took place. In the case of Engelking ('13), for example, not a trace of an ovary was found in an ovarian pregnancy which had become interstitial. Even without assuming the complete authenticity of this rather equivocal case, it would seem highly probable that the presence of ovarian tissue later in the pregnancy probably is determined very largely by the location of the fertilized follicle within, or by the exact location of the implantation upon the ovary.

Werth ('87) is said to have collected 12 cases, among which he regarded only that of Leopold ('82) as authentic. Leopold ('99) reported 14. Gilford ('01), in a splendid succinct review of the literature, gave 28 cases, 16 of which he regarded as undoubted and 12 as probable. Roche ('02) accepted only 12 cases, Füth ('02) accepted 21. Kantorowicz ('04), using the criteria of Leopold ('99), together with a microscopic examination as a basis, grouped the cases in the literature as

certain, probable, and uncertain. He considered 17 as certain, 10 as probable, and 13 as uncertain. And to the 17 cases regarded as certain by him, Kantorowicz then added two of his own, basing his decision, however, mainly upon the presence of decidua in the ovaries, thus making 19 cases regarded as authentic by him. Freund and Thome ('06) regarded 23 of all the cases reported up to that time as certain. Norris and Mitchell ('08) considered 16 as positive, 15 as probable and 9 as fairly probable. Warbanoff ('09) collected 34 cases and Norris ('09) regarded 19 of those contained in the literature of the previous decade as positive; but Williams ('10), from a critical review of the literature up to 1906, and upon the basis of the criteria of Spiegelberg, regarded only 13 as positive, 17 as highly probable, and 5 as probable. Mapes ('14) collected 30 cases, but wholly from secondary sources, and Lockyer ('17) 42, from the years 1910 to 1917. Of these cases Lockyer accepted 22 as authentic and 20 as questionable and undecided from the evidence available to him.

This short summary suffices to show that there is as yet no consensus of opinion as to what constitutes an ovarian pregnancy. Although this fact finds its explanation partly in our lack of sufficient knowledge, it is due also to the meagerness of some of the reports. Besides, if complete disintegration and lysis of intraovarian conceptuses can occur, then it must always remain a question of opinion in the future whether some of the cases so reported really were or were not true ovarian pregnancies. This must remain true no matter how thorough the microscopic examination, unless the clinical history or changes in the maternal organism can afford us crucial tests in such cases.

Anyone who reads far into the literature of ovarian pregnancy also must become aware of the fact that even very recently skepticism has been carried too far. Jacobson ('08), for example, placed the case of Kouwer-van Tussenbroek (a case which finally convinced Bland-Sutton) and that of Webster ('04) in the doubtful class! Furthermore, Jacobson also insisted upon the presence of an embryo or fetus as absolutely essential.

It must be emphasized, however, that even a liberal attitude on the part of a reviewer would not justify him in accepting all cases reported as genuine upon the basis of the reports themselves, for they—especially the older ones—often are too meager to enable one to form a reliable opinion. This is illustrated also by such recent reports as those of Garrard ('16), Martin ('17), Sweeney ('17), and of Mills ('17). Although it must be remembered that from the very nature of things it sometimes is impossible to make a report which in itself carries conviction, it is regrettable that in a number of relatively recent cases in which such a report apparently could have been made, this was not done. Mills' case seems to have been an instance of ovarian implantation in a region other than the Graafian follicle, and hence recalls the first case of Granville and the cases of Franz ('02), Norris ('09), Paucot et Debeyre ('13)?, and perhaps also that of Kouwer ('97) (van Tussenbroek, '99).

From evidence contained in the literature, it is clear that further reports of single cases are not needed for the purpose of emphasizing the occurrence of ovarian pregnancy, yet such reports nevertheless may help in the determination of the relative frequency of this novel and sinister condition, and also throw further light upon its genesis and the finer relations of the implantations, as well as upon other matters. Moreover, since the cases which are accompanied by a careful histologic examination and which for this reason alone are wholly unequivocal from an anatomic standpoint still are relatively few, the report of an additional case would seem to be justified. The present specimen (Carnegie Collection, No. 1522) was donated by Wynne to the Department of Embryology of the Carnegie Institution of Washington, and the following clinical report furnished by him:

CLINICAL HISTORY

GYN. No. 22303.—The patient, an Italian woman of 37 years, was admitted to the Gynecological Service of The Johns Hopkins Hospital July 12, 1916, complaining of pain in the lower abdomen, nausea and vomiting.

Family History.—Negative.

Past History.—General health good. She has never had any serious illness. For the past five years following a labor she has had recurring mild attacks of pain in the abdomen without nausea or vomiting.

Menstrual History.—Always regular every month except when pregnant or lactating. Duration four to five days; painless, moderate flow. Last period June 25, 1916. Last preceding period March 16, 1916. No intermenstrual bleeding before present illness.

Marital.—Married 18 years; seven children, oldest 16, youngest born 1½ years ago (died, 1915). Has had three miscarriages. History of labors and puerperia vague.

Present Illness.—Began five days ago (July 7, 1916) with sudden pain in lower abdomen, nausea and vomiting. She has had marked dysuria and painful defecation. For 12 hours after onset there was rather profuse bleeding from the vagina and there has been a bloody vaginal discharge since.

(The patient does not understand English and her husband acted as interpreter.)

Physical Examination.—T. 101.6° F. P. 96. R. 20. W. B. C. 8400. Hbg. 46 per cent.

The patient lies in bed grunting with pain. The skin is pale. The lips and mucous membranes are quite pale. There is a systolic blow heard at the apex and increasing toward the base, being loudest over the pulmonic area.

A drop of clear fluid was expressed from the right breast.

The abdominal respiratory movements are limited, although she does not complain of pain on deep inspiration. The flanks bulge somewhat. There is no demonstrable movable dulness. There is tenderness all over the abdomen, most marked over the lower left quadrant. There is increased resistance over the lower abdomen, but no muscle spasm. No masses can be made out.

There is a profuse bloody vaginal discharge. The cervix is pushed up behind the symphysis by a soft, exquisitely tender mass, filling the cul-de-sac. No crepitus is made out. Rectal examination confirms the vaginal. The fundus of the uterus is not felt.

July 13, 1916.—Ether examination.

There is a dark, bloody discharge from the vagina. There is no vaginal cyanosis. The cervix is lacerated, firm, and normal in size. The fundus of the uterus is about normal in size and is in anteposition. A boggy mass fills the cul-de-sac and to the right of the uterus a fairly firm mass, the size of a small orange, which is somewhat movable, can be felt. Definite blood-clot crepitus can be felt on rectal examination.

Pre-Operative Diagnosis.—Extra-uterine pregnancy, ruptured.

Operation (Dr. W. R. Holmes, Resident Gynecologist).—A free midline incision was made below the umbilicus. The peritoneum

was blood-stained. The abdomen contained 200 to 300 c. c. of dark fluid blood and clots, and a large clot filled the cul-de-sac. Active bleeding had ceased. The left tube and ovary were normal and free of adhesions. The right tube, which was quite normal in appearance, lay over a mass which had replaced the right ovary. This mass was roughly spherical, 5 to 6 cm. in diameter and semi-solid in consistency. Over the surface there were six or eight nodular projections, about 1 cm. in diameter. At the top of one of these projections there was a very small opening, from which bloody fluid could be squeezed. The surface of this mass was white with spots of bluish-black discoloration.

The appendix was normal except at the tip, where it was adherent to a blood-clot.

The tumor was removed by clamping, tying, and cutting into the right infundibulo-pelvic ligament and the right utero-ovarian ligament. The right tube was not removed. The appendix was also removed and all blood and clots were cleaned out of the abdomen. The incision was closed without drainage. At the close of the operation, the uterus was curetted. The uterine cavity measured 7.5 cm. in length.

A subcutaneous salt solution infusion was started on the table and continued on the ward until 2000 c. c. had been absorbed.

The patient was in good condition at the end of the operation and made an uneventful recovery.

The *urine* on admission contained red blood cells, white blood cells, no casts, acetone, a trace of albumin and no sugar. Several days after the operation it was negative, except for a faint trace of albumin.

August 2, 1916.—Discharged in good condition.

Gyn. Path., No. 22346.—Normal endometrium from curettage.

A letter from the patient dated February 12, 1918, said that she had remained in good health since the operation and had given birth to a full-term child January 29, 1918.

Several features in this clinical history deserve comment. First among these is the menstrual age as compared with the size of the chorionic vesicle. Since the cross-sections of the latter measure 15 x 18 mm. and since it and the amnion are degenerated and devoid of an embryo, it is evident that the latter must have died a good while before the time of operation. Hence, the menstrual period reported for June 25, 1916, very evidently was not the *last* period before pregnancy supervened, but the first period which recurred after the death of the conceptus. Consequently, this pregnancy undoubtedly dates from near April 13, the time of the first omitted period. Moreover, the conceptus must have died long enough before June 25 to have made inhibition of the succeeding period impossible. It should be noted, however, that the original menstrual cycle *apparently* was broken, for with the customary inter-menstrual period of 28 days, menstruation normally would have fallen due on June 7 instead of June 25. Hence, the maintenance of the original cycle would have brought rupture of this ovarian pregnancy, as indicated by the symptoms, on July 7, in direct relation with the onset of menstruation. Nor does it seem unlikely that the hyperemia accompanying the return of menstruation on June 25, if such it really was, may have been partly responsible for the onset of a sufficiently large and persistent hemorrhage to cause the slight rupture indicated by the symptoms on July 7. It must also be remembered in this connection that cases of ovarian pregnancy have been reported in which menstruation was uninterrupted. But in the case of Chiene ('13), for example, the death of the conceptus may have occurred so early that the succeeding period was not inhibited, and the same thing may be true of the case of Lea ('10).

Since the material from the curettage, done at the time of operation, showed the presence of a normal endometrium, the uterine decidua associated with this pregnancy must have been shed some time previously. Such a conclusion also would seem justified by the condition of the conceptus, which apparently was unable to prevent a return to the normal. The absence of decidua at the time of operation also suggests that what was reported as a return of normal menstruation on June 25 may have been hemorrhage accompanying the expulsion of the decidua.

Since, in the present case, the chorionic vesicle was so degenerated and so completely isolated in a large clot, and especially since no well-implanted villi were found in the sections and gross portions examined, it is not at all probable that the hemorrhage that caused the rupture was due to a contemporaneous invasion of the vessels by the fetal trophoblast, such as occurs in uterine and tubal implantations, and as has been actually described also in ovarian implantations by Franz ('02) and by others. In the present, and in similar cases in the literature, it would seem that hemorrhage was made possible also by degenerative changes in the highly vascular stroma of the ovary which had been greatly compressed and stretched by the proportionately large blood-clot, the organization of which would seem to have been precluded by its size alone.

The fact that relatively few unruptured ovarian pregnancies are recorded suggests that the old tenet that rupture is less likely the more advanced the pregnancy becomes, probably is open to serious doubt, as suggested by Banks ('12), who believed that the tubes can accommodate themselves more readily than the ovary. Banks stated that in the majority of cases of ovarian pregnancy rupture occurred in the first two or three weeks, and Caturani ('14) also expressed doubts regarding the dictum that rupture of the ovary is less likely the more advanced the pregnancy. No one will deny, I presume, that the symptoms of rupture may have been totally absent, as reported in the cases of Norris ('09) and Grimsdale ('13), but this does not imply that the ovarian stroma or the germinal epithelium still surrounded the full-term conceptus. Such an occurrence would be possible only if the ovarian stroma and the overlying germinal epithelium underwent an astonishing hyperplasia. Although such a thing is conceivable it is decidedly significant that no one has reported any such finding or observed the presence of mitotic figures.

Instead of undergoing hyperplasia the ovarian stroma in this case is found invaded, stretched, compressed, and degenerate, and the germinal epithelium is entirely absent. The fact that several observers have seen what they took for the fibrin layer of Nitabuch also shows that degenerative changes in the ovarian implantations may be extensive. Hence, it would seem to follow that the absence of symptoms of rupture merely may mean that the ovarian stroma and epithelium which happened to overlie the fetal membranes gradually have died and degenerated before being forced apart by the expanding conceptus or the increasing hemorrhage. That such

a sequence of events is possible would seem to be undoubted, and merely distension of the ovarian stroma until it completely surrounded a full-term pregnancy is hardly conceivable; whereas, the absence of pain upon the yielding of an exceedingly thin degenerate layer of ovarian stroma is quite conceivable.

That rupture may occur very early is exemplified also by the cases of Chiene ('13), Seedorff ('15), and especially by that of Anning and Littlewood ('01) and of Holland ('11). In such curious instances as that of Grimsdale ('13) one can hardly assume that the ovarian tissue was preserved about the entire conceptus, and it is not at all unlikely that full-term ovarian pregnancies, which, according to Warbanoff, supplied a surprisingly large percentage of all cases collected by him, will form a far smaller percentage in the statistics of the near future. Indeed, they already form a far smaller percentage of those reported up to the present, and the advances in diagnosis alone make it very unlikely that in the future many cases of ovarian pregnancy will advance far before being detected.

The present specimen, which had been hardened and cut before it came to my attention, is a firm, nodular, dark-colored mass, 26 x 16 x 11 cm., shown in Fig. 1. In the gross, it especially recalls the specimens of Freund and Thome, Giles ('14-'15), Jaschke ('15), and Lockyer's ('17) second case. The exterior is smooth though bosselated and formed by a rather injected layer which is extremely thin, showing the blood-clot beneath, around the greater extent of the specimen. The surface layer is eroded over several small elevated areas in which the blood-clot underneath is exposed. Hence, the capsule may have been ruptured in several or only in one of the areas as noted at the time of the operation. Near the region of amputation through the mesovarium shown to the right in the figure and marked by the corrugations of the hemostat, the tissue overlying the clot becomes more opaque, thicker, and also more yellowish. Here it is studded with small cysts, the character of which in itself suggests ovarian tissue. The color of the area to the right also is suggestive, and the cysts later were found to contain a clear viscid fluid, so characteristic of cysts of the ovary. The location of the main portion of the ovarian stroma shows that implantation occurred near the mid-point of the free convex or posterior border of the ovary, and that the stroma forming the sides gradually was forced apart, not by the growing conceptus, except perhaps at the beginning, but mainly by the hemorrhage itself.

The major portion of the surface of the divided specimen shown in Fig. 2 is composed of blood-clot, the presence of which confirms the "blood-clot crepitus" spoken of in the history. This clot contains an empty vesicle, the wall of which is formed for the greater part of its extent by a thin fibrous layer, except near the proximal or lower portion in the figure, where a thicker portion of ovarian tissue hoods the clot. Approximately only about one-third of the ovarian stroma seems to be preserved.

Near the exterior of the thicker portions of the latter, a small cyst with clear content is found directly beneath the surface, as indicated in Fig. 4. The distal or upper portion in the figure shows the clot to contain an empty, smooth-walled, degenerate chorionic vesicle, such as is frequently seen in tubal clots.

Examination of the cut surface with the binocular microscope shows the presence of only a few isolated, degenerated, and some hydropic villi scattered through the clot. Examination of the chorionic vesicle shows the presence of only a few attached villi and that the amnion is fused to the chorion. Since the entire specimen obtained at operation is still covered by a layer of ovarian tissue which is unbroken save in a few very small areas, it is evident that we are dealing with a very good example of an undoubted ovarian pregnancy in spite of the absence of an embryo. The latter undoubtedly did not escape through the small rupture in the capsule, for the chorionic vesicle seems entirely intact. Although the absence of a corpus luteum in the opposite or left ovary was not especially mentioned, lack of comment would seem to suggest that none was present, for the ovary very evidently was examined. Hence, this implantation probably took place within the Graafian follicle itself, and not in some other area of the ovary.

Celloidin sections of the excised portion show that the blood-clot contains no fibrin and that it is composed of relatively fresh and fairly well-preserved blood in the region near the main body of the ovarian stroma. The latter is quite normal although decidedly vascular, and contains ova. The layer of the ovarian stroma which surrounds the clot becomes thinner and thinner the nearer the free border is approached. It also becomes more trabeculated, hemorrhagic and degenerate. No overlying layer of smooth muscle, as mentioned by Young and Rhea ('11) and also by Kantorowicz, was seen. Some infiltration with polymorphonuclear leucocytes is noticeable. Degenerate villi are scattered about in the blood and a few others are apparently still attached to the equally degenerate ovarian stroma. Trophoblast is absent on these, although some of the villi that lie isolated in the clot possess a very evident epithelium and also are associated with a few small masses of very degenerate syncytium. Only a few degenerate nonvascular villi are still seen on the chorion. Very little evidence of epithelial proliferation is present on these, despite the fact that the blood in which the vesicle is embedded is not very degenerate. This seems to suggest that the hemorrhage which caused the rupture of the ovary was comparatively recent, although the conceptus had been dead for some time. Some of the villi scattered about in the blood-clot are outlined by degenerate syncytium only, and nothing but small degenerate masses of the latter are seen on the chorionic membrane or lying about isolated in the degenerate blood found in other places. Nevertheless, the epithelium of the chorionic vesicle is thickened at several points. The amnion is fused with the chorion and both membranes are very degenerate and destroyed almost completely in several places. The surrounding ovarian tissue, which is markedly vascular and degenerate, shows infiltration in places, especially where it is stretched over the large clot. No fibrous layer bounds the implantation cavity, as in the case reported by Seedorff. The ovarian stroma merely

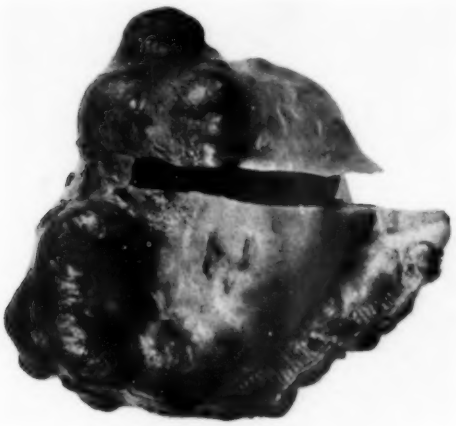

FIG. 1.—External appearance of the reconstituted gross specimen (Carnegie Collection, No. 1522). Natural size.

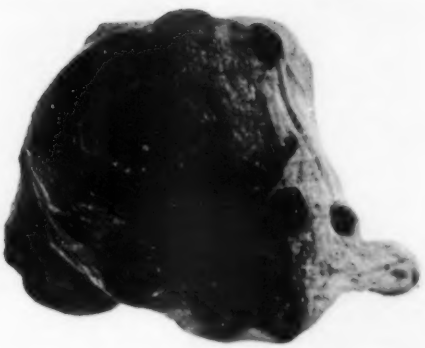

FIG. 2.—Appearance of cross-section of specimen shown in Fig. 1. ×1.

FIG. 3.—Photograph of a section from a part of the specimen showing the clot largely surrounded by ovarian stroma and containing the empty vesicle. The arrow points to the portion near which degenerate masses of what may have been lutein cells are found. × 2.

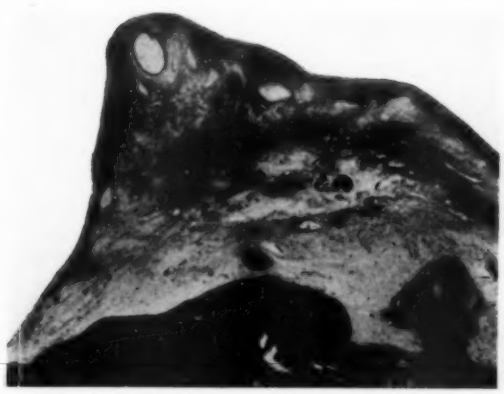

FIG. 4.—Photograph of a section taken from the thick portion of the ovarian stroma near the mesovarium, showing a well-developed Graafian follicle. × 3.

is slightly condensed here and there, and in places contains areas of hyaline degeneration, the exact origin of which could not be definitely determined. A few of these are found near the thin bounding layer of the ovarian stroma, but no lutein layer or even luteal cells could be recognized. The only objects seen which might be regarded as possibly luteal in origin are two microscopic rhomboidal areas which lie near a small depression upon the surface, indicated in Fig. 3. These areas, which were covered by a very thin layer of ovarian stroma only, were made up of parallel, degenerate, slightly separated cords consisting of a syncytium containing numerous rather pycnotic unequal-sized nuclei. No pigment was seen in these areas, and were it not for the arrangement of the syncytial cords, one would not be reminded even remotely of a possible luteal origin. Although the germinal epithelium was wholly absent in the areas examined, these questionable areas nevertheless may have had such an origin. In the absence of lutein cells the present case corresponds to that of Freund and Thome and others, and stands in marked contrast to the case of van Tussenbroek, Franz, Anning and Littlewood ('01) and Thompson ('02). As in the case of Seedorff, no decidua was present and nothing suggestive of an attempt at decidual formation, as reported by Franz, Webster ('04 and '07), and by Caturani and Kantorowicz, was seen in the portions examined.

In describing his case, Seedorff declared that in some places of contact between the fetal and maternal tissues he could not discriminate between trophoblast and connective-tissue cells which looked like decidual cells and lutein cells. It is interesting that Sudorff also spoke of villi which were almost filled with Langhans' cells, an observation which naturally makes one wonder whether by any possibility these could not have been Hofbauer's cells.

The preserved ovarian tissue which was found near the amputation stump contained hemorrhagic follicles, as observed also by Mall and Cullen ('13). A Graafian follicle 3 mm. in section, shown in Fig. 4, protruded above the rest of the stroma and was quite mature. The presence of this follicle might be taken as an evidence of the occurrence of ovulation during pregnancy, were it not for the fact that the presence of so degenerate a conceptus shows that as far as any effect upon the maternal organism was concerned, the pregnancy virtually had been terminated long before. That both ovulation and menstruation can and do return after the death of an ovarian conceptus, but before its removal from the ovary, is illustrated also by cases in the literature, especially by that of Norris ('09). One must assume, however, that few, if any, surviving fetal elements can be present under these circumstances. This conclusion also would seem to be confirmed by the remarkable case of Sencert and Aron ('14). These authors reported a case of ovarian pregnancy in which nothing but a portion of an umbilical cord 5 mm. long containing Wharton's jelly, two arteries and a vein, and what was regarded as a placenta, remained. The latter was said to be composed of a narrow layer of plasmodium and a much thicker layer of trabeculated syncytial trophoblast containing blood between the trabeculæ.

Because of the singular structure of this placenta and also because of the failure to find villi or any remnant of the membranes, the authors concluded that the chorionic vesicle therefore could not have reached the villous stage. How such a supposition can be reconciled with the survival of a portion of an umbilical cord entirely normal in structure, it is difficult to see. The ovary concerned was brown, of the size of a "large fresh walnut," and contained a tumor, apparently the so-called placenta, which was 2 cm. in diameter. Although these fetal remnants had brought about not only almost complete amenorrhea for two years and also atrophy of the ovary and uterus, ablation of the affected ovary was followed not only by a return of the menses, but by a normal pregnancy within seven months.

A second instance of ovarian pregnancy of special interest was that of Giles. No fetus was found, although the pregnancy was unruptured, and Giles estimated that the conceptus had died in the third or fourth week. The operation was not done until five months after the onset of the pregnancy. What is particularly interesting in this case is that Giles speaks of the mucoid degeneration of the connective tissue of the villi. The latter were found to be large, much branched, and had ramified in the clot. Since Giles also spoke of one of the illustrations as showing a vascular state of some of the villi, it seems possible that this was a case of hydatiform degeneration, even though there were no signs of activity of the syncytium. Since the fetal membranes were isolated in a blood-clot very much degenerated and the villi without a Langhans' layer, one scarcely could expect to find much evidence of epithelial proliferation so common (but not essential) in hydatiform degeneration. Giles estimated that four months had elapsed since death of the conceptus, and if this specimen really was a hydatiform degeneration, it is the first one observed in ovarian pregnancy and hence of particular interest for this reason alone.

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GRANVILLE SHARP PATTISON[1]

By William Snow Miller, University of Wisconsin

Gross, in his biographical sketch of Pattison, says:

> It is no exaggeration to say that no anatomical teacher of his day, either in Europe or in this country, enjoyed a higher reputation; his forte as a teacher consisted in his knowledge of visceral and surgical anatomy, and in the application of this knowledge to the diagnosis and treatment of diseases and of accidents, and to operations.

Being a man of intense feeling and strong prejudices he did not easily brook opposition. Because of these characteristics the early years of his career were stormy and his reputation as a teacher was fully acquired only after many bitter controversies, one of which was so acrimonious that it was fought out on "the field of honor."

The year of Pattison's birth is usually given as 1791, but he says in his "Refutation," addressed to Dr. Nathaniel Chapman, of Philadelphia, under date of November 28, 1820, "I shall soon enter on the 28th year of my age"; this apparently makes 1793 the more correct date. He died November 12, 1852, after a short illness, of obstruction of the ductus communis choledochus.

[1] Read before The Johns Hopkins Hospital Historical Club, December 2, 1918.

GRANVILLE SHARP PATTISON.
Courtesy of Dr. J. M. H. Rowland.

NATHANIEL CHAPMAN.
Courtesy of Dr. Howard A. Kelly.

Granville Sharp Pattison was the youngest son of John Pattison, of Kelvin Grove, Glasgow. Of his early education we know nothing except the statement that he was probably educated at the University of Glasgow. That he was a hard-working student is shown by his being, when but 18 years old, assistant to Allen Burns, and on the death of Burns, in 1813, becoming his successor to the Chair of Anatomy, Physiology and Surgery in the Andersonian Institution, a recently organized medical school in Glasgow. Here he made quite a reputation as a lecturer, and had it not been for his naturally indolent nature and love of ease, would, no doubt, have attained in his later years preëminent reputation as an anatomist.

In November, 1818, charges were brought against him by Dr. Ure, one of his colleagues, of having committed adultery with his wife, and a divorce was obtained by Dr. Ure on that ground. The divorce laws of Scotland were at that time peculiar; all divorce procedures were brought in the consistory court, which was an ecclesiastical organization. It was not necessary that the parties charged with adultery had ever seen each other and the reputed paramour might not have ever existed. In any event, the accused paramour could not appear and defend himself. If the husband obtained a divorce from his wife on the ground of improper conduct, he could immediately bring a second action for damages and the accused party could then appear in court and endeavor to disprove the charge.

This second action was never instituted by Dr. Ure. After the arrival of Pattison in this country, Dr. Ure attempted to publish an octavo volume dealing with the case. One of his witnesses, however, having confessed that her declaration was false and that she had been induced to make her statements by means of threats and bribes, Dr. Ure suppressed the volume, for he could not sustain his charges, and had he attempted under these circumstances to circulate the publication he would have subjected himself to criminal prosecution. This episode was unfortunate for Pattison and it played an important rôle in the turbulent years which followed; for, although generally known to be unfounded, many years elapsed before it ceased to be recalled.

In Glasgow the charge was generally discredited, for Dr. Ure did not possess an enviable reputation; in fact, a statement is made that he barely escaped transportation to Botany Bay "for fraudulently stealing and destroying his father's will." In spite of this accusation Dr. Ure retained his position in the Andersonian Institution. Pattison explains the situation in the following statement:

The Andersonian Institution of which Dr. Ure is a member is an establishment of late date. The funds which were obtained for the erection of its buildings were procured by subscription; and as Dr. Ure was very active, at the time when the money was raised, in obtaining it, and granted to the subscriber of £20 a perpetual ticket of admission to one of the courses of his lectures, it has become a question, whether the money was bestowed on him as an individual, he granting personally an equivalent, or to the Corporation of the Institution.

When Dr. Ure, about six years ago, fraudulently stole his father's will for the purpose of defrauding his family, an attempt was made to expell him from the institution; but as the Trustees, upon taking advice, learnt that his expulsion would involve them in a tedious litigation, a litigation which would require to be carried on by money advanced by them as individuals, the attempt was abandoned.

Replying to this, Dr. Chapman shows that the institution was *incorporated* on June 9, 1796; when the buildings were ready for occupation he does not state, but he does infer that Pattison was guilty of a misstatement in that he considered an institution 21 years old as an "establishment of late date." The founder of this Institution was John Anderson, a Scottish naturalist, who in his will provided for its establishment; he died January 13, 1796, and the incorporation on June 9, 1796, was undoubtedly the first step in carrying out the provisions of the will. The medical department gave its first courses in 1799.

Dr. Chapman attempts to offset the statement in regard to the will of Dr. Ure's father by saying:

Not long before he came to this country, Mr. Pattison was tried for a felony, in stealing a body from the grave. . . . . Mr. Pattison merely escaped from want of evidence that he had taken the clothes of the deceased: the part of the offence most penal under the Scotch law.

In this instance Pattison was in the best of company, for John Hunter, Sir Astley Cooper and nearly every teacher of anatomy up to the passage of the "Anatomy Act" in 1832, might with more or less justice be termed an "acquitted fellon."

The occasion of Pattison's coming to Philadelphia was the expectation of occupying the Chair of Anatomy in the Medical Department of the University of Pennsylvania, made vacant by the death of Professor Dorsey and temporarily filled by Prof. Philip Syng Physick. That he was given to understand before leaving England that the position was open to him is certain, but that this was unofficial is also certain.

On December 24, 1818, Pattison received a letter from his brother, John Pattison, who at that time resided in Philadelphia, in which he states that his legal adviser, Mr. Chauncy, agreed with him that there was an opportunity for a man of talent to be appointed to the position left vacant by the death of Dr. Dorsey. The fact that he was a foreigner was certainly against him, but he was "inclined to think that the trustees will be more guided by talent, than by any other consideration." He advised that letters be obtained from Astley Cooper and others and "you had better say the extent of your museum, etc., which I know Mr. Burns considered invaluable."

Under date of April 20, 1819, Dr. Dewees, of Philadelphia, wrote Pattison a letter which contained the following statement:

I have, contrary to any right, taken the liberty to advise upon the subject. As far then as a firm belief that you would succeed (and that belief founded on pretty certain data) will offer an inducement to pay us a visit, I have no hesitation to declare, that no question remains in my mind, that were you on the spot, your election would be certain. It is unquestionably the opinion of two of the most influential and best informed men here. Your visit should be as prompt as possible, that you might have the necessary time for the preparatory arrangements here. My opportunities

to judge of the sentiments of those, who have this gift in their power, will be best explained by your brother.

Acting on this advice Pattison arranged his affairs as quickly as possible and sailed from Liverpool for New York, where he landed July 6, and on the evening of July 7, 1819, reached Philadelphia.

The two "most influential and best-informed men" referred to above were Drs. Chapman and Physick. Each of these denied having authorized the use of his name. Chapman states:

The trustees, after postponing the appointment for six months . . . . had publicly advertised that they would receive applications from any quarter. But we soon discovered our mistake—for at their first meeting which took place not many days afterwards, when all the testimonials of Mr. Pattison were submitted to them, so far from a favorable impression being made, these recommendations were treated contemptuously, as extravagant and hyperbolical—it being quite manifest, that no individual with half the merit which they set forth, would sacrifice his actual possessions, to embark in so adventurous a scheme!

Chapman evidently forgot that Philadelphia and the country in general was peopled with those who had left the old country and settled in this country because they thought that they had here an opportunity to improve their condition—that they were adventurers.

Shortly before sailing, while he was in London, Pattison was made a member of the Medico-Chirurgical Society of London and a Fellow of the Royal College of Surgeons. Had there been the stain on his character which was charged against him, it seems doubtful if these honors would have been bestowed on him. The "testimonials" were written by Prof. John Barclay and Dr. Thompson, of Edinburgh; Francis Jeffrey, editor of the *Edinburgh Review;* James Wardrop and Astley Cooper, of London; the Rev. Dr. Love, of Glasgow, a celebrated clergyman of the Kirk of Scotland; Sir James McGregor; Sir William Adams; and others.

Just at this time there was a good deal of intrigue taking place in the faculty of the University of Pennsylvania, and in 1819 Philip Syng Physick,

Yielding up his own better judgment to the schemes of others, for perhaps the first time in his life, allowed himself to be transferred—for the act was not of his own choice—from the chair of Surgery, to that of Anatomy, from the place where he was emphatically *at home*, to one in which he was *comparatively a stranger*.

Pattison did not accept any appointment in the University, though one was offered to him; he also declined a professorship in the Transylvania University at Lexington, Ky. Chapman makes Pattison's declination of the call to Lexington appear in a false light and says:

The College, were, moreover, as I am told, justly indignant at the disrespectful manner in which they were treated, considering the only motive of Mr. Pattison, in procuring the appointment, was to have it published as an early recognition of his consequence in this country.

He also states that Dr. Caldwell was furnished with all of Pattison's documents, and had a distinct understanding with Pattison that if he were elected he would accept. If such were the case, Dr. Caldwell would not fail to make mention of it in his "Autobiography," for such episodes as this are favorite themes in his narrative. A careful reading of Peter's "History of the Medical Department of Transylvania University" also fails to reveal a single reference to this incident.

In 1820 Pattison was elected Professor of Surgery in the University of Maryland, and he looked forward to leaving behind him all the intrigue and malevolence he had encountered at Philadelphia, fostered in a large degree by Dr. Nathaniel Chapman. This did not materialize, for

One of the faculty, a Professor in the University of Pennsylvania! came to Baltimore immediately after my settlement in that City, apparently for the purpose of shutting me out from the hospitality of the citizens, by the most foul, the most malignant, the most false asperations against my character.

The animosity existing between Pattison and Dr. Chapman, who seems to have been the moving spirit in the campaign against Pattison, soon reached an acute stage and Pattison issued a challenge to Dr. Chapman, which he did not accept. This led Pattison to go to Philadelphia, and on October 23, 1820, he put up in two public places the following post:

To the Public

Whereas Nathaniel Chapman, M. D., Professor of the Theory and Practice of Medicine in the University of Pennsylvania, etc. etc. has propagated scandalous and unfounded reports against my character; and Whereas when properly applied to, he has refused to give any explanation of his conduct, or the satisfaction which every gentleman has a right to demand, and which no one having any claim to that character can refuse, I am therefore compelled to the only step left me, and Post the said Dr. Nathaniel Chapman, as a liar, a coward and a scoundrel.

Granville Sharp Pattison.

Following the European custom Pattison resolved to stay two days in Philadelphia; but, he says:

My stay, however, was not long left to my option. . . . . I was arrested at 11 o'clock A. M. of the day on which I had put up the post. Dr. Chapman denies all agency in the matter, be it so.

When the case came before the grand jury, all the correspondence in the case was furnished by Chapman, and Pattison says:

Perhaps he did this that I might be convicted, in order that an opportunity might be furnished him of displaying his *generosity* and magnanimity, by applying "instantly in person to the Executive" for my "pardon."

In his letter refusing to meet Pattison, Chapman gives as his reason, "the character and conduct of Mr. Pattison, as well in relation to the causes which compelled him to leave Scotland, as to events which have subsequently happened." Not satisfied with this, in November, 1820, Chapman issued a pamphlet in which he attempts to justfy his conduct. To this Pattison replied in a like manner November 28, 1820. Pattison "had the good fortune and address to enlist the sympathy of his colleagues and a large part of the community in Baltimore in his behalf, and presenting his side of the case to a committee of prominent citizens, he was exonerated from all blame."

This was not Chapman's first "affair"; he had some years before challenged Dr. Dewees. In regard to this affair Chapman says:

It happened fifteen or sixteen years ago; and if my conduct was reprehensible, I hope I have since atoned for it, by a friendship warm, cordial and sincere. What, however, will be thought of the malignity of a man, who thus endeavors to disturb the happiness of families, by references of this nature! ! !

Pattison replying to this does not put Chapman in an enviable light:

I have not a "numerous family," I admit, and here I allow there is a distinction. But did Dr. Chapman before he had a family, when he challenged Dr. Dewees, who had a numerous one, think this excused him?

The quarrel between Chapman and Pattison was finally taken up by General Thomas Cadwalader, Dr. Chapman's brother-in-law, and four years after Pattison's arrival in this country (1823?) they met somewhere in Delaware. Cadwalader received the ball from Pattison's pistol in his "pistol arm" which was disabled thereby during the remainder of his life. Pattison was uninjured, "but a ball passed through the skirt of his coat near the waist."

In 1826 Pattison resigned his professorship at Baltimore and returned to England. Why he resigned a position which with his professional services he states was bringing him $10,000 a year is not clear; for, as a teacher, he had a successful record while in Baltimore, and the University of Maryland enjoyed its greatest prosperity. On the one hand, is the statement that he "led a very gay life" in Baltimore and that his health was thereby impaired and that after he left it was doubtful whether he recovered; on the other hand, there is Pattison's flat denial and 26 additional years of active life.

In July, 1827, Pattison was appointed Professor of Anatomy in the newly organized University of London. Before long he became involved in difficulties, different from those at Philadelphia, but equally disastrous. Pattison was a Scotchman and had taught in Scotland and "America"; he had introduced as a text-book Fyfe's anatomy, written by a Scotchman: he had for his demonstrator a Mr. Bennett, an Englishman, who had conducted a school of anatomy in Paris which had, very properly, been refused credit at an English institution: he had incurred the displeasure of Wakley, editor of the *Lancet*, who supported Bennett; but chief of all he was a Scotchman. If any one doubts the attitude of London at this time towards Scotchmen let him read Pichot's "Life and Labors of Sir Charles Bell" and the "Letters of Sir Charles Bell" by his brother George.

Wakley began his attack on Pattison by a sharp criticism of Fyfe's anatomy; it must be acknowledged, however, that the criticism was justified. Wakley was a friend of the medical students and supported them in most of their complaints and, possibly, prompted some of them. That he was responsible for many reforms in medical instruction and medical practices is to his credit, and he deserves all the credit accorded to him, but he sometimes overshot his mark; take, for example, his attitude towards Sir Charles Bell, Marshall Hall, and others who have left an honored name and life work.

On July 23, 1831, Pattison was dismissed from the Chair of Anatomy at the University of London. The events preceding and following his dismissal are full of interest. Clarke, in his "Autobiographical Recollections of the Medical Profession," says:

No matter what a man's talents and acquirements might be, he had little or no chance of advancement at a Hospital, except through family or money influence. All the prizes in the Profession were monopolized by those who could pay for them, or who were fortunate enough to have friends at Court. The apprentice of the Hospital Surgeon paid a very large premium for his indentures, and, as a rule, it was understood, that he was to be placed on the Hospital staff as part return for his money outlay. This gave rise to a system of nepotism of the most objectionable character: Hospital Surgeons were selected, not from the mass of the Profession, but from the private pupils and relations of the "staff." . . . .

To add to the discontent prevailing, there had been (1827) an unseemly quarrel at the great Hospital of St. Bartholomew's, in which Mr. Abernethy did not bear an enviable part. . . . . At this time, too, the establishment of what was then called the "University of London" attracted increased attention to the system of nepotism. . . . . The announcement of the names of Professors of this Institution startled the Profession by the fact that most, if not all but one of them, were "outsiders"; were not, in fact, connected with any of the large endowed Hospitals, but were all of high and deserved distinction.

The first name on the list given by Clarke is that of Pattison.

In the issue of the *Lancet* for March 5, 1831, there is a communication signed "A Senior Student of the London University" in which an attempt is made to show that Pattison is unworthy of his professorship and that Bennett should have the position. Much of "Senior Student's" complaint and most of the student dissatisfaction is based on the fact that Pattison attempted to enforce discipline in his classroom. That Wakley had previous knowledge of what was taking place in Pattison's lecture room is shown by the following quotation from the above-mentioned communication:

You are already, Sir, aware of the proceedings which were instituted during the last session by a part of the medical students against one of the lecturers upon anatomy, Mr. Pattison.

This communication was replied to by another student, who signs himself "Veritas," under date of March 7, 1831, and throws considerable light on the case. One of the charges brought against Pattison in the original complaint was "that the defect in his articulation rendered him unfit for the chair." This charge was afterwards erased. It is interesting to note that this is identically the same charge brought by Wakley against Sir Charles Bell. "Veritas" says "a more unkind and unfeeling imputation could not have been made." Toward the close of his reply "Veritas" says:

Picture to yourself, Sir, an assembly of mere youths, many of whom have just commenced their studies, met together to decide upon the ability or inability of a professor who was engaged in teaching anatomy before many of them had an existence. The very idea is preposterous.

He goes on to say that he has attended two sessions of Pattison's lectures and has always found them instructive and any one who pays attention to his lectures "cannot fail of reaping abundant store of anatomical knowledge."

As stated above, Pattison was dismissed July 23, 1831. The resolutions passed by the Council show that they finally yielded to the student clamor; but

In taking this step the Council feel it due to Professor Pattison to state, that nothing which has come to their knowledge, with respect to his conduct, has in any way tended to impeach either his general character, or professional skill and knowledge.

One member of the Council protested vigorously, but vainly, against Pattison's dismissal and enumerates eight reasons why he should not have been dismissed. In the seventh item the statement is made that the other professors testified to the excellency of Pattison's qualifications and that "many of them had expressed their firm conviction to the Council, that the dissensions in the medical school did not arise out of any defect or misconduct of Professor Pattison." They evidently had in mind outside influences.

From this time until the end of the controversy in the *Lancet* the discussion was confined mainly to Wakley and Pattison, with now and then short communications from some of Wakley's friends. The final shot was fired by Pattison and his closing paragraph is exceedingly interesting reading:

In the letters of Drs. Turner and Thompson, and in your "strictures" on my Statement, the fact of my having been a successful teacher in the United States is treated with great contempt. "It does not follow" observes Dr. Turner, "that he could succeed in London because he was successful in America." The Americans, forsooth, are easily satisfied. It is very well for John Bull to say so. I should, however, have expected that you were too well informed as to the state of medical science in the United States, to have given currency to such a vulgar and unfounded prejudice. The Americans, I assert, are as far advanced and as enlightened in their medical opinions as any country in Europe: and I would further assert, without the fear of contradiction, that there may be numbered amongst the medical profession of that country, gentlemen who, for extent and profundity of knowledge, and for capacity of conveying instruction, have no reason to fear comparison with the most eminent teachers in Europe. Let the improvements in medical and chirurgical science be reviewed for the last thirty years, and it will be found that America has furnished her full quota.

This defence of American medicine and American medical men by one who had good reason for resentment shows Pattison to have been a man of more character than is generally acknowledged.

Shortly before Pattison was dismissed from the Chair of Anatomy Bennett died and the Committee of Education of the University of London looked about for a new professor. They were fortunate in their selection, for they recommended Mr. Jonas Quain for the professorship and his brother, Mr. Richard Quain, for demonstrator, and peace reigned for the time being.

Pattison was not long without a professorship, for in 1832 he took up his duties as Professor of Anatomy in the Jefferson Medical College, in Philadelphia, where he met with immediate success. He held advanced ideas as to the best way in which anatomy should be studied, as the following abstract from the annual announcement of the Jefferson Medical College for the year 1832 shows:

Anatomy, the basis of all medical reasoning, can only be studied *practically* during the term of the student's attendance on lectures. Should he neglect his opportunities for acquiring a complete knowledge of the science during the term passed by him at college, he must be content to continue forever afterwards a mere driveller in his profession. Now, anatomy is not to be learnt by an attendance on lectures. Dissection, and dissection alone, can make a man an anatomist. The Professor of Anatomy, it is true, may, by animated and masterly demonstrations, do much to guide and assist the anatomical student in true prosecution of his studies, but it is in the dissecting room, with the dead body before him, by patient and assiduous dissections, that the student can alone acquire a knowledge of anatomy.

Pattison remained in Philadelphia until 1841, when he joined in founding the Medical Department of the University of New York. Here he held for the remainder of his life the Professorship of General Descriptive and Surgical Anatomy.

With his return to this country, the strife and turmoil of his life very largely disappeared. He married a Scotch lady by the name of Sharp, who was possessed of some fortune. I have been unable to ascertain the date of their marriage, but it proved to be a very happy one, for Gross gives a pleasing picture of their domestic life. He was social, ever ready to do a kind act, a lover of the beautiful in nature and art. He took an active interest in establishing the Grand Opera House in New York. He also was an enthusiastic disciple of Izaak Walton.

Pattison was the author of "The Register and Library of Medical and Chirurgical Science." He edited with notes Burns' Surgical Anatomy of the Arteries of the Head and Neck, Masse's Anatomical Atlas, and Cruveilhier's Anatomy; he was one of the editors of the *American Medical Recorder*, a journal which contains many of his contributions to medical literature.

NOTES

Pattison's Exoneration.—All the facts concerning the divorce obtained by Dr. Ure were laid before the managers of the Andersonian Institution by James Burn, "Writer of the Signet," and Pattison was completely exonerated by them.

Pattison's Museum.—Cordell states that this "was extensively advertised in the medical journals and newspapers of the country." After he went to the University of Maryland he exerted a considerable influence in the councils of the University and he eventually induced the University to purchase it for $8000, and in 1821 a new building (Practice Hall) was erected for its accommodation. It consisted "of upwards of 1000 selected morbid and healthy specimens, and in variety, excellence and number was far superior to any other in America." For some time it constituted the chief attraction for visitors to the University. Many of the preparations are still extant, but in a somewhat neglected condition.

Dr. Physick's Transfer to Anatomy.—Chapman made the statement to Pattison that he thought by transferring Dr. Physick to the Chair of Anatomy and by bringing Dr. Gibson from Baltimore to occupy the Chair of Surgery the changes "would operate beneficially in two ways. It would strengthen the University of Pennsylvania, and at the same time weaken that of Maryland." This was before Pattison received his call to Baltimore.

Position Offered at the University of Pennsylvania.—The position offered Pattison at the University of Pennsylvania was to be shared with another, and he did not care to accept such an arrangement. He therefore began to give independent lectures on anatomy and surgery and he says that he had "a class of above one hundred and ninety students." The hour of Pattison's lecture was fixed after consultation with Chapman and was one which Chapman assured Pattison would not conflict with any of the professors. When, however, Chapman learned that Pattison's lectures were popular with the students he changed the hour of his own lecture to that used by Pattison and thus prevented the students from attending Pattison's lecture.

Gibson-Pattison Controversy.—Apparently no one in Philadelphia knew of the particular structure demonstrated by Pattison. Gibson, however, found in Colles' Surgical Anatomy "an unusually full and well-written account of those very parts, which Mr. Pattison had claimed as a discovery of his own." Like many another worker Pattison thought he had found something new, but as soon as he found he had been anticipated he withdrew all claims of discovery, only claiming that certain post-operative results were best explained by the presence of this structure (Colles' fascia).

Gibson's Characteristics.—"He was very vain in his personal appearance, and more so of his reputation as a surgeon and teacher of surgery. His style of lecturing was easy, agreeable, and instructive, but he never omitted an opportunity to set forth his own merits and to depreciate the ability of surgeons whom he disliked. He was especially vindictive against his leading rival in Philadelphia." In 1847 Gibson was in Europe and returned late in the fall with a wardrobe of broadly striped waistcoats and trousers to match. These he displayed to his class until the lot was exhausted, causing much merriment in the class-room and prolonged rounds of applause which he received as evidence of his personal popularity (Busey, U. P., 1848). Dr. S. D. Gross says, "Gibson was not an amiable man. His ill temper often betrayed him into unkind expressions, even in the lecture room."

During his last illness Gibson sent for Gross. "My acquaintance with him was slight, and I was therefore not a little surprised when I received a message to visit him at his country residence. An old friend, to whom I mentioned the fact, exclaimed, 'Don't you know that he has no friends in the medical profession of Philadelphia.'"

Pattison's Brogue.—"What added interest to the speaker was a slight lisp and a Scotch accent, which never entirely forsook him, despite his efforts to overcome them in early life" (Gross).

Chapman as a Teacher.—"A cleft palate, with its consequent indistinct utterance, robbed him of every charm as a teacher, for which his vast experience, great learning, and qualities of heart and mind so well fitted him. The most careful attention, near and in front of him was necessary to catch the words as they were spoken, except by those who by long experience had become accustomed to his unfortunate and defective enunciation" (Busey, U. P., 1848).

He (Chapman) "has seen several cases of hydrocephalus in girls about the age of puberty, caused by metastasis of action from the uterus to the brain."

Chapman believes "many cases that have a decided character of angina pectoris afterwards terminated in well-marked gout cases. A gentleman long afflicted with this affection had gout induced in his extremities by the use of sinapisms, and the former affection was relieved; but, improperly removing the sinapisms, the disease suddenly returned to its place and immediately killed him."

Epilepsy, "usually assigned to a certain state of the nervous system—a peculiar sensibility or irritability—it is the temperament of genius and intellect—Julius Cæsar, Mahomet, Napoleon, etc." (From bound volume of MS. notes taken by James C. Hall (U. P., 1827) of Chapman's lectures delivered in 1826.)

Pattison's Resignation from the University of Maryland.—Pattison, in his "Statement of Facts in his connection with the University of London," says that it was his intention to return to the States and deliver another course of lectures; instead of doing this he spent some time in Germany. I have tried to ascertain the date of his resignation, but have been unsuccessful. This might help by showing that he resigned from the University of Maryland to accept the position in the University of London.

Pattison's Resignation from the University of London.—The only medical man who was a member of the Council of the University of London (Dr. Birkbeck) supported Pattison and opposed Mr. Bennett and the way in which Bennett was appointed. I do not think that Pattison, at the time he wrote his "Statement of Facts," realized the extent of Wakley's opposition and influence. Later he understood it better and gave it proper consideration.

Defense of American Medicine.—Medicine in the United States 1800 to 1830. Pattison, in the closing paragraph of his final communication made the statement that if the advances in medicine and surgery "be reviewed for the last thirty years, it will be found that America has furnished her full quota." I have had the curiosity to look up American medicine during this period and find abundant material to substantiate his affirmation.

In Boston, there was John Warren and J. C. Warren, eminent as anatomists and surgeons—the latter founder of the Massachusetts General Hospital; James Jackson in internal medicine and Jacob Bigelow, who published in 1820 his "American Medical Botany"—his essay "On Self-Limited Diseases" did not appear until 1835. In New York, Wright Post and Valentine Mott were doing pioneer work in surgery. In Philadelphia, there was Casper Wistar and W. E. Horner in anatomy; Philip Syng Physick in surgery; John C. Otto in clinical medicine (he was the first to describe hemophilia); J. K. Mitchell in neurology; W. P. Dewees in obstetrics; Nathaniel Chapman in the theory and practice of medicine. In Connecticut, Elisha North was introducing vaccination, recommending the use of the thermometer in fevers and in 1817 established the first eye infirmary in the United States.

Nathan Smith was establishing medical schools in New England and furnishing the entire faculty; he was a pioneer operator for ovariotomy and, in 1824, published his essay on "Typhus Fever," now a medical classic.

In the West there were four men who have made a name in American medicine, Ephraim McDowell, B. W. Dudley, William Beaumont and Daniel Drake. McDowell is known the world over as the father of ovariotomy (Nathan Smith did not know of his operation when he operated in 1821). Dudley was famous in his day for his success in lithotomy. Beaumont, in 1825, began those studies on digestion which he gave to the world in 1833. Drake was establishing medical schools and publishing essays on medical education in the *Western Journal of the Medical and Physical Sciences;* at the same time he was preparing for his great work, "Diseases of the Interior Valley of North America."

Other names could be added to this list, but it is unnecessary. I consider the point raised by Pattison well proven.

Has the Parotid Gland Ever Been Extirpated?—The Professor of Surgery at the University of Pennsylvania (Dr. Gibson) in a clinic at the Philadelphia Alms House, open to students of the Jefferson and the University, referred slightingly to the claim of the Professor of Surgery at Jefferson (Dr. McClellan) that he had performed the operation (under a general attack on Sir Charles Bell who had made the same claim). He refers to Bell as a *Canvasback duck* more worthy of his gun than *the Dipper* (Dr. McClellan).

Pattison took up the challenge and made a reply which was brilliant for its wit and sentiment and convincing with its weight of learning. In the same publication Pattison ridicules the story that he was so ignorant of the subject that he mistook the omohyoid muscle for the carotid artery and was about to ligate it

when one of his students called his attention to the mistake and, being set right by his pupil, found the artery and tied it.

I have tried unsuccessfully to ascertain what were the relations between Chapman and Pattison after his return to Philadelphia as Professor of Anatomy at Jefferson. Dr. J. W. Holland, of Philadelphia, made inquiries for me of a distant relative of Dr. Chapman and reported that "he does not know a living soul who could state what were Chapman's relations to Pattison in later years." As nothing further appears in print, the animosities of earlier years seem to have died out and disappeared.

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COMMENTS ON THE PATHOLOGY AND BACTERIOLOGY OF FATAL INFLUENZA CASES, AS OBSERVED AT CAMP DEVENS, MASS.

By S. Burt Wolbach, Boston

Death from influenza means death from lung complications—pneumonia in some form. The pathological picture of the lungs as seen in a series of postmortems is a kaleidoscopic one. At first it was most difficult to correlate the various gross findings, and it also has been difficult to correlate the microscopic findings, and this part of the work is not yet completed. I have had the advantage of comparing my observations with those of Dr. Goodpasture at the Naval Hospital at Chelsea, Mass., and again with a study of the series of cases we have had at the Peter Bent Brigham Hospital in Boston, and it now is possible to give a fair account of the probable sequence of events and to explain the apparent great differences in the pathology.

In a series such as is presented here two types of lungs stand out as strikingly characteristic findings in this disease. The first is encountered in those cases in which death has occurred within a few days after the onset of pulmonary signs. These cases yield lungs which are partially collapsed, dark red, lax, but meaty in consistency. The pleural surfaces are often partly covered with a dusky red mottling, due to small extravasations of blood beneath the serous coat. There may be a thin layer of dusky red fibrinous exudate upon the pleural surfaces, particularly over the posterior borders. On section these lungs are dark red and wet. They are dripping wet, and the fluid from some portions is a blood-tinged serous liquid and from others dark red and bloody. On close inspection the cut surfaces are usually found to be thickly sprinkled with air vesicles of considerable size. The lung tissue as a whole, after the liquid has drained from it, is brownish-red in color, and somewhat translucent and friable. The mucosa of the bronchi is usually very dark red in color, and the bronchial lymph nodes are enlarged and deep red in color.

The other type of lung, which is found in patients that have lived for 10 days or more after the onset of the disease, while showing traces of the type of lesion just described, is characterized by a very extensive bronchitis, with broncho-pneumonia, discrete or confluent, and peri-bronchitis. These lungs are more voluminous than the preceding, but they do not fill the chest cavity at postmortem. They are nodular, and the pleural surfaces occasionally show a striking tracery, due to the injection of the sub-pleural lymphatics. Portions of the surfaces of the lungs may be covered with a thin layer of fibrinous exudate. On section the most prominent feature is the extensive injection of the bronchi, particularly the smaller ones, with a fibrino-purulent exudate. The injection of the bronchi may be so extensive and uniform as to produce geometrical patterns, which are very striking when the condition is accompanied, as it usually is, by a marked infiltration of the inter-lobular septa. A casual inspection suffices to show that the smaller bronchi are distended, usually markedly dilated, and in cases of two weeks' duration spherical and cylindrical bronchiectases are very common. The gross appearances of this type of lung are very much like those described by Dr. MacCallum in pneumonias after measles. The condition in fact

is one of pan-bronchitis; peri-bronchitis with extensive infiltration of the interlobular septa; and organization in alveoli and bronchioles.

These two predominating types on first consideration seem to represent different processes. I hope to show convincingly that they simply represent different stages of the same process. Before I undertook the study of the Camp Devens cases I had some experience with influenza pneumonias at the Peter Bent Brigham Hospital, and I have since quickly surveyed the material obtained there during the time I was at Camp Devens. The Brigham Hospital cases, on the whole, have been quite different in their gross appearances. On the other hand, the cases at the Naval Hospital in Chelsea have been very similar to those at Camp Devens, and I think a cross-section of the study of one series of cases is very much like that of the other—to which Dr. Goodpasture agrees. There are many other interesting features of the pathology of the lungs, such as the rapidity with which bronchiectasis occurs and the large number of cases which develop interstitial emphysema, and of course the consequences of both of these conditions; bronchiectatic abscesses and gangrene of lungs from the first, emphysema of the mediastinum and subcutaneous emphysema from the second. Of this series of 28 postmortems, done between the 2d and 32d day of the disease, there were six that showed subcutaneous emphysema; eleven showed emphysema of the mediastinum.

In comparing notes with other pathologists one is struck by the differences in gross appearances of the lungs in different localities. The same is true in regard to the bacteriology. The table which accompanies this report shows the very high percentage of pure *Bacillus influenzæ* pneumonias at Camp Devens; again, a similarity with the series at the Chelsea Naval Hospital as reported by Keegan. However, in the Camp Devens series there were a few cases in which the hemolytic streptococcus and the pneumococcus were found, and these lungs presented different gross appearances. In a cursory analysis of the Brigham Hospital cases autopsied (about 30), I find a predominance of hemolytic streptococcus and pneumococcus lungs. Without going into corroborative details at this time, I may say that in the gross appearance of the lungs I have laid emphasis upon, *B. influenzæ* was the only organism which could be cultivated and I unhesitatingly associate these distinctive conditions with that organism. In lungs showing other types of solidification, other organisms were responsible for the exudation characterizing the pneumonias. The hemolytic streptococcus, the staphylococcus and the pneumococcus, each produces its distinctive picture, the last often that of lobar pneumonia.

While the bacteriological evidence, based upon the assumption that *B. influenzæ* is the cause of influenza, is very good in support of the stand that there is a distinctive lung lesion in these influenza pneumonias, the histological study has afforded very definite proof. Early in this study of the Camp Devens cases, I recognized the fact, as have others, that a striking type of reaction was present, a condition of acute alveolar emphysema with the deposit of a hyaline fibrinous material on the alveolar walls. The intervening alveoli are compressed and filled with exudate, which in the early cases is largely serous or bloody, containing but little fibrin. It is this acute alveolar emphysema, with the serous and hemorrhagic exudate, that gives the characteristic gross appearance to the lungs in the early stage of the disease. In order to determine how common this lesion is, I have gone over all of the Brigham Hospital autopsies on influenza cases, and find it to be constant. It may be masked by a pneumococcus or streptococcus exudation or by extensive hemorrhage, but its presence can always be determined by the finding of the hyaline fibrin outlining greatly distended air spaces in the lungs. It is the one distinctive feature in the pathology of influenza pneumonias, and its constant occurrence is indicative of the entity of the initial lung infection. The interpretation of this lesion was not easy. The hyaline fibrin, because of its prominence and the juxtaposition of cellular exudate, often simulates the outlines of alveoli. As a matter of fact, it outlines cavities filled with air, which may or may not completely fill groups of alveoli. Although alveolar walls in contact with this fibrin may be necrotic, tissue elements play no part in its formation. A similar hyaline fibrin was found in two cases of emphysema of the mediastinum where the mediastinal areolar tissues were infected by pneumococcus, secondary to pneumococcus pericarditis. The physical characteristics of this fibrin are determined by its contact with air, and an important factor is probably the mechanical compression of strands of fibrin by air. What is the source of the exudation in the alveoli in these early pneumonias? The exudation may be present in alveoli with intact walls, or walls showing very slight reaction, mainly evidenced by activity of the respiratory epithelium. In all cases severe lesions were found in the finest bronchioles, and in the alveolar ducts. The latter show an exudation composed mainly of polymorphonuclear leucocytes and small quantities of fibrin. The walls are filled with leucocytes, and are often necrotic in places. The intralobular bronchioles show severe lesions of the mucosa, and it is often possible to demonstrate the source of hemorrhages from capillaries. The obvious explanation, and indeed the only possible one from the material at hand, is that the major injury is to the bronchial system, and mainly in the finest bronchioles and alveolar ducts. To secure the degree of emphysema present it is necessary to assume a valve action of the exudate in the bronchi. The character of the hyaline fibrin deposit around air vesicles and upon the alveolar walls suggests a pouring of exudation into the alveoli from the bronchioles and alveolar ducts, at a time when air is able to pass. Thus the patient is virtually blowing bubbles in his own lungs, into a medium of exudation relatively poor in fibrin.

The mechanism of interstitial emphysema formation is easily seen, where the greatly distended alveoli are in contact with the pleura of interlobular septa. In these locations it is possible to demonstrate rupture of the alveolar walls and the direct continuity of fibrinous strands, partially filling clefts dissected by the air from alveoli to pleural or interlobular connective tissue. A series of gross sections and microscopic sections from lungs with interstitial emphysema shows that the air finds the easiest route of exit from the lung in the con-

nective tissue surrounding blood-vessels. It dissects along blood-vessels to the hylus of the lung and from there along the great vessels and bronchi into the mediastinum, over the pericardium into the anterior mediastinum, and upwards along the trachea into the tissues of the neck, whence it escapes into the subcutaneous tissues. This subcutaneous emphysema may appear very early, as will be seen by the accompanying chart. The earliest case was seven days from the first symptom, which means, of course, a shorter duration of the lung involvement. The majority of the cases were noted on or after the 10th day from the initial symptoms of the disease.

It must be borne in mind in considering the pathology of these lungs, that the lesions are not uniformly distributed, and therefore very extensive injury in portions of one or several lobes are compatible with life for a considerable period of time. The bronchial lesions apparently progress, and may extend throughout the whole of one or both lungs, producing the anatomical picture of the more chronic cases, that of a panbronchitis with bronchiectases and peri-bronchitis. During this period of extension in bronchi, a number of things may happen to the portions of the lungs first involved. They may become secondarily infected with pneumococcus or streptococcus, or the Gram-negative diplococcus called by English workers "Diplococcus mucosus." In rare instances Staphylococcus and Friedlander's bacillus have been encountered. The fate of the tissue depends on the nature of the infecting organism; as, for example, fibrinous exudation with the pneumococcus and abscess formation with the staphylococcus. In a number of instances these portions of the lungs, severely damaged at the onset, did not become secondarily infected; at least, these lungs have shown only the influenza bacillus at the autopsy, and have undergone extensive organization resulting in cicatrices of large sizes. If we take a series of lungs which have shown only the influenza bacillus in cultures and in sections, we may still have all the stages described exclusive of those with secondary infection, and accordingly we must conclude that the reaction to the influenza bacillus is less intense in the later stages of lung involvement than in the earlier. This is shown best in comparing two lungs from the same case, where in one lung, usually the right, we find the severe damage of the early lesion with bronchiectasis and peri-bronchitis, and in the other lung a much less intense bronchial reaction, with much less marked peri-bronchitis, or none at all. The involvement of the pleura in lungs infected solely with the influenza bacillus is very slight. There are hemorrhages into the pleura and perhaps a thin layer of fibrin upon the surface. The amount of fluid in the pleural cavities was always small, though blood-tinged. Empyema was found in cases secondarily infected with the streptococcus or pneumococcus. The involvement of the pleura may result from the extension of the inflammatory process along the interlobular septa and lymphatics, or, and this I believe is more commonly the case, from bronchiectatic cavities situated close to the pleural surface.

Gangrene of the lung was noted in one of the Camp Devens series in a case showing very extensive bronchiectases, with bronchiectatic abscesses. Extensive necrosis of the lung has been observed in a number of cases in this same series and at the Brigham Hospital—necrosis due to organisms other than the influenza bacillus.

Organization in the pure *B. influenzæ* cases was a common end result. The organization of the exudate begins early, certainly before the 10th day of the disease, and a prominent factor in bringing about this result is, I believe, the plugging of the bronchi with exudation. In patients who had survived three weeks or more there were very complicated gross appearances, due to extensive cicatrization of large portions of the lung. The contraction of interlobular septa, due to the avascular organization of exudate, causes marked distortion of the lobules of the lung, and peculiar lines of retraction on the pleural surfaces.

It is not the purpose of the present report to include the whole pathology of influenza. There are a few interesting features in other organs which are worthy of emphasis, however. Eight of the Camp Devens series showed waxy degeneration of the rectus muscles, and subsequent experience at the Brigham Hospital indicates that it was probably overlooked in some of the earlier postmortems done at Camp Devens. A number of these cases showed rupture and extensive hemorrhage into the rectus muscle. This lesion has been noted in other muscles; for instance, the transversalis, the internal and external oblique muscles, the latissimus dorsi, the pectoralis major and the intercostal muscles. The testes occasionally showed minute petechiæ, but on the whole no striking gross change was observed. Microscopically very striking changes were encountered in nearly every case, namely, the cessation of activity in the seminiferous tubules; actual degenerative changes were frequently noted, and in late cases beginning fibrous tissue replacement of the degenerated tubules. This lesion of the testes seems to be wholly a toxic one, as there is very little cellular reaction. It is difficult to understand why such severe toxic lesions of the muscle and testes should occur, in the absence of effects attributable to toxins in other organs. For instance, the reaction of the spleen is very slight, the heart muscle rarely has shown any gross or microscopic lesion, and in general seems to escape entirely the toxic effect of the disease. Lesions of the adrenal, when extensive, such as hemorrhage, can be attributed to secondary infection, usually the hemolytic streptococcus. Minor acute lesions are constantly found in the cortex in influenza cases, but these lesions are similar to those found in many infectious diseases—the disappearance of lipoid content, and focal necrosis with mononuclear phagocytic cell reaction. The head was opened in 20 of these cases. Infection of the middle ears was found in 13. Infection of the sphenoidal sinus in 20, frontal sinus in seven, and of the ethmoidal cells in eight cases. The bacteriology of the sinuses is given in the chart. Three cases showed punctate hemorrhages in the cerebral cortex.

BACTERIOLOGY

I do not intend to discuss at length the bacteriology of the epidemic. The table is a true account of the findings, and I prefer to have individuals draw their own conclusions. The opportunities for bacteriological work were particularly good.

CAMP DEVENS AUTOPSIES

No.	Duration	Type of lung	Remarks	Bacteriology	Sections
201	2 days.	Edema and congestion.	Purpuric rash.	Lung = No growth.	Skin = Streptococci in vessel thrombi. Lung = Streptococci in polys in bronchi.
183 * *	7 days.	Lobar (?) Bloody. Bilat. solidification.	Subcut. emphysema. No head.	Lung = Pure *B. influenzæ*.	*B. influenzæ* only in bronchi and alveoli.
203 *	7 days.	Bilat. lobar.	Waxy deg. rectus abd. Sph. } Sinusitis. Eth. }	L. L. = *B. influenzæ* + hem. strep. R. U. = *B. influenzæ* + hem. strep. R. L. = *B. influenzæ* + hem. strep. Sph. Sinus = *B. influenzæ*. Pneumococcus IV.	Streptococcus.
207	8 days.	Lobar—left lower.	Fibrinous pleuritis. Fibrinous pericarditis. No head.	L. L. = Pneumococcus II. R. L. = Pneumococcus II.	Pneumococcus.
216	8 days.	Broncho-pneumonia, wet—bloody.	Waxy deg. rectus abd. Sph. Sinusitis.	L. U. L. L. R. U. R. L. } No growth.	Large gram-positive cocci.
188	9 days.	Bilat. lobar.	No head.	Lung = Pneumococcus.	Pneumococcus.
197 *	9 days.	Bilat. broncho-pneumonia, confluent on right. Bronchiectasis.	Sph. Sinusitis.	L. L. = *B. influenzæ* + pneumococcus. R. M. = *B. influenzæ* + pneumococcus. R. L. = *B. influenzæ* + pneumococcus. Sph. sin. = *B. influenzæ* + pneumococcus.	*B. influenzæ*. Pneumococcus. Flat diplococci, Gram-negative.
192 * *	10 days.	Bilat. confl. broncho-pneumonia. Bronchiectasis.	Emphysema of media. Empyema, right 400 c. c. No head.	L. L. = *B. influenzæ*. R. U. = *B. influenzæ*. R. L. = *B. influenzæ* + pneumococcus.	L. L. R. U. } *B. influenzæ*. L. U. R. L. = *B. influenzæ* + pneumococcus.
195 * *	10 days.	Bilat. broncho-pneumonia. Confl. on left lower. Bronchiectasis.	Bilat. otitis media. Sph. } Sinusitis. Eth. }	L. L. = *B. influenzæ*. R. L. = *B. influenzæ*. Sph. sin = *B. influenzæ* + pneumococcus IV.	*B. influenzæ* present. Predominating organism a Gram-negative diplococcus.
202 *	10 days.	Bilat. broncho-pneumonia.	Subcut. emphysema. Focal encephalitis. Otitis media. Sph. sinusitis. Waxy deg. Rectus abd.	L. U. = Staphylococcus aureus. L. L. = *B. influenzæ*. Gram-negative diplococcus. R. U. = As above. R. L. = As above. Sph. sin. = *B. influenzæ* + pneumococcus. Mid. ear = *B. influenzæ* + pneumococcus.	*B. influenzæ* in bronchi. Gram-negative diplococcus found in superimposed exudate upon older broncho-pneumonia.
198 * *	12 days.	Bilat. broncho-pneumonia.	Emphysema of media. Otitis media. Fr. } Eth. } Sinusitis. Sph. } Waxy deg. rectus abd.	L. U. = *B. influenzæ*. L. L. = *B. influenzæ*. R. L. = *B. influenzæ*. Sph. sin. = *B. influenzæ*. Fr. sin. = *B. influenzæ*.	*B. influenzæ* predominates. Gram-negative diplococcus found in some sections.
193 * *	13 days.	Confl. bilat. broncho-pneumonia. Bronchiectasis.	Subcut. emphysema. Fr. } Sph. } Sinusitis. Eth. } Waxy deg. rectus abd.	L. U. L. L. R. U. } No growth. Sph. sin. = *B. influenzæ* + pneumococcus IV.	*B. influenzæ* in small numbers in two lobes. *B. influenzæ* + large cocci, in two lobes.
204 * *	13 days.	Bilat. broncho-pneumonia. Bronchiectasis.	Subcut. emphysema. Otitis media-bilat. Sph. } Eth. } Sinusitis. Waxy deg. rectus ab.	L. U. L. L. R. U. R. L. } No growth. Sph. sin. = *B. influenzæ*. Hem. strep. Pneumococcus IV. L. mid. ear = *B. influenzæ*. Hem. strep. Pneumococcus.	*B. influenzæ* in small numbers in bronchi.

CAMP DEVENS AUTOPSIES.—*Continued*

No.	Duration	Type of lung	Remarks	Bacteriology	Sections
214 *	13 days.	Lobar—rt. lower. Fibr. pur. bronchitis. Bronchiectasis.	Pneumococcus meningitis. Fr. / Sph. / Eth. } Sinusitis. Bilat. otitis media.	L. L. = { *B. influenzæ*. / Pneumococcus. R. L. = { *B. influenzæ*. / Pneumococcus. Sph. sin = { *B. influenzæ*. / Pneumococcus.	Rt. lower = Pneumococci. L. Lung = { *B. influenzæ*, great numbers in bronchi. / Pneumococci in alveoli.
186 *	14 days.	Bilat. broncho-pneumonia. Bronchiectasis.	No head. Subcut. emphysema.	Cultures lost.	*B. influenzæ*. Streptocci. Large cocci.
215 * *	15 days.	Bilat. confl. broncho-pneumonia. Bronchiectasis.	Otitis media-bilat. Sph. sinusitis.	Lung = No growth. Sph. sin. = *B. influenzæ*. Fr. sin. = *B. influenzæ* + strep.	*B. influenzæ* in great numbers, pure.
211 * *	17 days.	Bilat. broncho-pneumonia. Bronchiectatic abscesses.	Otitis media-bilat. Sph. sinusitis.	L. U. = *B. influenzæ* + pneumococcus. L. L. = *B. influenzæ*. R. U. = *B. influenzæ* + pneumococcus. R. M. L. = *B. influenzæ*. R. L. = *B. influenzæ* + pneumococcus. Sph. sin. = lost.	*B. influenzæ* pure, great numbers except in bronchiectatic abscesses and according to lobes. *B. influenzæ* + pneumococcus in bronchiectatic abscesses.
212 *	20 days.	Bilat. broncho-pneumonia. Gangrene R. L.	Cerebral abscesses. Spleen abscesses. Otitis media-bilat. Fr. / Sph. / Eth. } Sinusitis.	Fr. sin. = *B. influenzæ* + pneumococcus II. R. M. E. = *B. influenzæ* + pneumococcus II.	Bacteria of all sorts.
219 * *	21 days.	Broncho-pneumonia—rt. Bronchiectasis.	Emphysema of media. Empyema-bilat. Veg. endocarditis-mitral. Otitis media-bilat. Sph. sinusitis.	No cultures. 9½ hours postmortem.	*B. influenzæ* in great numbers in alveoli and bronchial exudate. Mixed bacteria in bronchiectatic cavities.
223 * *	22 days.	Bilat. broncho-pneumonia. Bronchiectasis.	Fibrinous pleuritis. Chr. otitis media-bilat. Fr. / Sph. / Eth. } Sinusitis. Waxy deg. rectus abd.	No cultures. 12½ hours postmortem.	*B. influenzæ* in great numbers in alveoli and bronchial exudate. Occasional diplococcus.
226	22 days.	Bilat. broncho-pneumonia, advanced organization. Bronchiectasis.	Emphysema of media. Chr. otitis media-rt. Chr. sph. sinusitis.	No cultures. 13½ hours postmortem.	No bacteria except in granulating walls of bronchi, here pneumococcus.
218 * *	23 days.	Organizing broncho-pneumonia. Bronchiectasis.	Organizing pleuritis. Sph. Sinusitis.	R. U. = *B. influenzæ*. L. L. = *B. influenzæ*. R. L. = *B. influenzæ*, rare col. L. U. = No growth. Sph. sin. *B. influenzæ* and pneumococcus.	*B. influenzæ* present. Pneumococcus predominates.
224 * *	26 days.	Organizing bilat. broncho-pneumonia.	Emphysema of media. Chr. otitis media-left. Sph. sinusitis. Waxy deg. rectus abd.	L. U. = *B. influenzæ*. L. L. = *B. influenzæ*. R. U. = *B. influenzæ*. R. L. = *B. influenzæ* + pneumococcus.	*B. influenzæ* (one slide).
227 * *	30 days.	Organizing bilat. broncho-pneumonia.	Fibrinous pleuritis-rt. Sph. / Fr. } Sinusitis. Otitis media-bilat.	L. L. = Contam. R. U. = *B. influenzæ*. R. M. = *B. influenzæ* + pneumococcus. R. L. = *B. influenzæ* + pneumococcus.	*B. influenzæ* in bronchi (four slides).
194 *	31 days.	Confl. bilat. broncho-pneumonia. Bronchiectasis.	Otitis media bilat. Sph. sinusitis.	L. L. = Hem. strep. R. L. = *B. influenzæ* + hem. strep. Sph. sin. = *B. influenzæ* + strep.	Streptococcus. *B. influenzæ* (one of seven slides).
213 * *	32 days.	Collapsed lungs, negative.	Empyema-bilat. Veg. endocarditis. Waxy deg. rectus abd. No head.	L. L. = *B. influenzæ*, pure. R. L. = *B. influenzæ*, pure. Pericard. = pneumococcus II.	*B. influenzæ* in bronchi and alveoli. Pneumococci in bronchi.
225 *	?	Lobar—L. upper. Gray hepatization.	No head.	No cultures. 12 hours post mortem.	*B. influenzæ* in bronchial exudate. Pneumococcus.
191	12 days.	Confl. bilat. broncho-pneumonia.	No head. Subcut. emphysema.	Lung = No growth.	

FIG. 1.

FIG. 2.

FIG. 4.

FIG. 3.

FIG. 6.

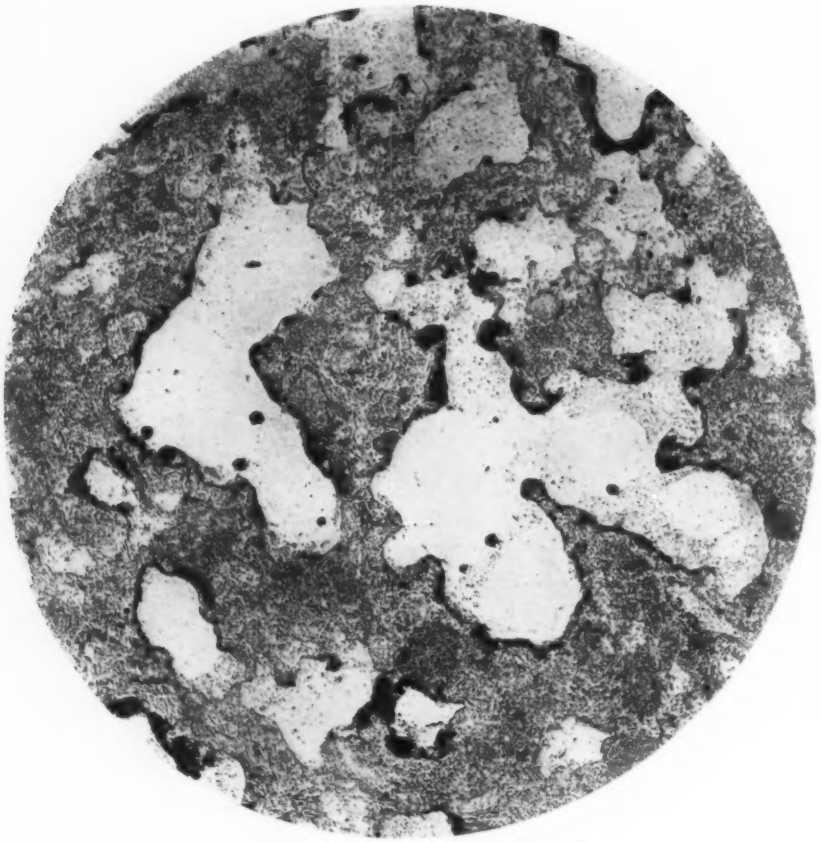

FIG. 5.

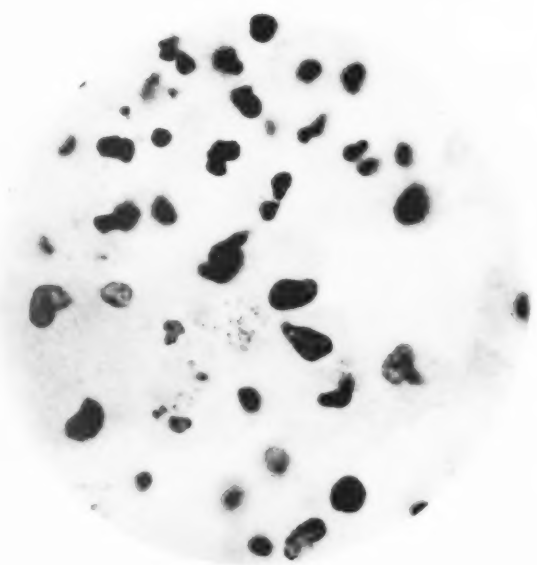

FIG. 7.

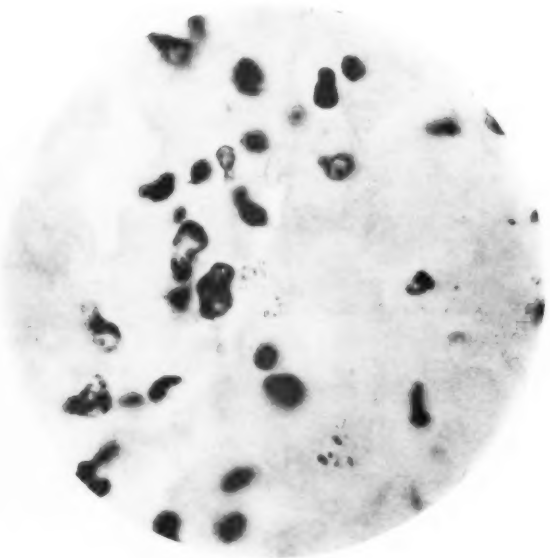

FIG. 8.

as the postmortems were done within a few hours after death and the cultures were made and studied by myself. The bacteriological findings were further controlled by staining sections of the lungs for bacteria, the method employed being that of Giemsa. Because of their small size the influenza bacilli are easily recognized. It is interesting to note that in some early cases the bacilli were found not only in the bronchial exudate, but in the submucosa of bronchi and in the alveolar walls of the lung. Inspection of the chart will show that the influenza bacillus was found in pure culture in one or more lobes in nine of the 23 cases from which cultures were made. In sections of lungs from cases in which no cultures were made, influenza bacilli were found apparently pure in two cases, and mixed with other organisms in one case. In one case no influenza bacilli could be found. There were two cases of lobar pneumonia and one case with gangrene of the lung in which no influenza bacilli were found. Of 28 cases by cultural and histological methods combined, *B. influenzæ* was demonstrated in 23 cases, and in 14 of these in pure culture. It is worthy of note that the bacilli were present in pure culture in a number of the late cases. In a number of cases in which influenza bacilli were not found in the lungs by culture, they were found in cultures from the sinuses of the skull or from the middle ear.

An analysis of the table of bacteriological results shows that the bacteriology of the lungs was mixed in a significant number of cases, but it also shows that the one organism occurring with greatest constancy, and in practically every case, was the influenza bacillus. We may regard the pneumococcus, streptococcus, pneumobacillus, and the various micrococci encountered, as secondary invaders, without reasonable doubt. But are we justified in so regarding the influenza bacillus? It is extremely difficult to account for the epidemiological features of this pandemic if we accept the bacillus influenza as the cause. Our lack of knowledge of the pathogenicity of the influenza bacillus and our failure to reproduce the disease in man and animals with pure cultures is also a strong argument against its being the cause of influenza. Yet, on the other hand, it is almost as difficult to explain the constant occurrence of the influenza bacillus in a series such as I have studied. One must keep in mind that our means of identifying the influenza bacillus are meager and that so far but few diagnostic criteria are available; and, by analogy, it seems almost certain that a group of organisms may exist having similar cultural and morphological properties, as is the case with the pneumococci.

The pathology of the lungs indicates clearly that we are dealing with a specific infection with a distinctive pathology in its early stages. The occurrence of *B. influenzæ* in pure cultures in the early stages is a fact of importance in the consideration of the etiology of influenza and I believe firmly establishes the existence of a *B. influenzæ* pneumonia.

EXPLANATION OF CHART AND FIGURES

Chart.—The following abbreviations are used:

L. U. = Left upper lobe.	Sph. = Sphenoid.
L. L. = Left lower lobe.	Eth. = Ethmoid.
R. U. = Right upper lobe.	Bilat. = Bilateral.
R. M. = Right middle lobe.	Confl. = Confluent.
R. L. = Right lower lobe.	

The stars in the first column indicate the presence of *B. influenzæ* in the lungs; double stars, in pure culture in one or more lobes.

Fig. 1.—Photograph of a Kaiserling specimen showing acute interstitial emphysema, characteristic of the early lesion in uncomplicated influenza pneumonia. Case 195.

Fig. 2.—Photograph of a Kaiserling, specimen showing uncomplicated influenza pneumonia, of 17 days' duration. Case 211.

Fig. 3.—Photograph of a Kaiserling specimen of uncomplicated influenza pneumonia, of 26 days' duration. Note the extensive cicatrization with bronchiectasis. Case 224.

Fig. 4.—Interstitial emphysema in uncomplicated influenza pneumonia, of 13 days' duration. Case 204.

Fig. 5.—Low power photomicrograph, from an uncomplicated early influenza pneumonia, of 10 days' duration. Case 192.

Fig. 6.—Uncomplicated influenza pneumonia, of 17 days' duration, with extensive organization. Case 211.

Fig. 7.—Clump of influenza bacilli in alveolar exudate, early influenza pneumonia. Case 183.

Fig. 8.—Influenza bacilli in alveolar walls, early influenza pneumonia. Case 183.

PUBLICATIONS.

The following eight monographs:

Free Thrombi and Ball-Thrombi in the Heart. By J. H. Hewitt, M. D. 82 pages. Price, $1.00.

Benzol as a Leucotoxin. By Laurence Selling, M. D. 60 pages. Price, $1.00.

Primary Carcinoma of the Liver. By M. C. Winternitz, M. D. 42 pages. Price 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By Frederick L. Hoffman, LL.D., F.S.S. 161 pages. Price, $2.00.

The Origin and Development of the Lymphatic System. By Florence R. Sabin. 94 pages. Price, $2.00.

Venous Thrombosis During Myocardial Insufficiency. By Frank J. Sladen, M. D., and Milton C. Winternitz, M. D. Price, 75 cents.

Leukaemia of the Fowl: Spontaneous and Experimental. By Harry C. Schmeisser, M. D. Price, $2.00.

The Structure of the Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. By O. Van Der Stricht and T. Wingate Todd. Price, $2.00.

are now on sale by The Johns Hopkins Press, Baltimore. Other monographs will appear from time to time

PROCEEDINGS OF SOCIETIES

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

NOVEMBER 18, 1918

1. **Clinical Observations on Epidemic Influenza.** Dr. A. L. Bloomfield and Dr. G. A. Harrop.

   Published in the Bulletin, January, 1919.

2. **Comments on the Pathology and Bacteriology of Fatal Influenza Cases, as observed at Camp Devens, Massachusetts.** Dr. S. B. Wolbach, Boston.

   Published in the present issue, page 104.

DISCUSSION

Dr. S. Burt Wolbach.—There are a few points in the preceding paper by Dr. Bloomfield with which I wish to take issue. I believe that influenza is a disease of the respiratory tract; that in the respiratory tract we have the distinctive pathology of influenza. I believe that nearly every disease has somewhere in the body a lesion, and a fairly distinctive lesion, connected with it, and that the seat of infection in influenza is the respiratory tract. To explain the early involvement of the sinuses of the skull, for instance, we must regard them as part of the respiratory tract; at least the mucosa is in direct continuity with that of the respiratory tract.

In some localities, particularly the Naval Hospital in Chelsea, they have had a higher percentage of pure cultures of influenza bacillus than my series shows, and I think it is difficult to explain why the influenza bacillus happens to be the only invader of the lung in such a large proportion of cases. I dislike very much to go into reasons or evidence, in the lack of proof, but my own work has forced me to the conclusion that influenza is a disease of the respiratory tract, and that this is the one part of the body where the lesion constantly occurs; but I shall not advance arguments one way or the other in regard to the etiology of influenza. As a matter of fact, I do not believe that any argument regarding the habits of the influenza bacillus in culture tubes or in tissue, or in association with other bacteria, is worth a great deal, but I think the reasons are many for believing that we may have to deal with a particularly virulent strain of influenza bacillus. We are all familiar with the variation in behavior of strains of streptococcus, such as occur in milk-borne epidemics, where the streptococcus achieves extreme virulence. The fact that there has been in the neighborhood of Boston during the past few years a number of small epidemics of streptococcus infection may explain the large number of influenza cases complicated with the hemolytic streptococcus that we have had at the Brigham Hospital. I have already said that we know very little about the influenza bacillus, and I feel that I have presumed a great deal in identifying certain organisms as influenza bacilli, but according to our present knowledge they must be classified as such. They all have a certain morphology, they all are Gram-negative, they require hemoglobin for cultivation, they will not grow in ordinary media or at room temperature, and though I place some value on their behavior in association with other bacteria, I feel that all of our criteria taken together are indeed very slight for the identification of the influenza bacillus.

I feel somewhat secure in the position I have more or less arbitrarily taken this evening for purposes of discussion, and for which I think I have considerable evidence, though the evidence is not proof. I should feel much stronger in my position that the influenza bacillus is the cause of influenza were it not for the fact that I have had small chance to investigate the early type of extensive lung involvement with positive bacterial findings. This is a weak point in such evidence as I have.

Dr. W. W. Ford.—I would like to say a word or two about some of the points referred to which have been interesting us in the bacteriological laboratory of the School of Hygiene. One of the first statements to be made in regard to the influenza bacillus was that this epidemic was occasioned apparently by an organism which was different from the influenza bacillus which has been isolated from time to time from various cases during the past 10 years—an organism which differed somewhat from the clear-cut influenza bacillus which we have come to regard as typical.

It is interesting to note that in the large series of cultures of the influenza bacillus my associate, Mr. Robinson, has been receiving from Washington, organisms isolated from the present epidemic, one can make out about as many variations in morphology as those shown by the organisms isolated before the epidemic. At first, the cultures seemed to be clearly and unmistakably different, and yet from good photographs and drawings it is evident that the variations of morphology are quite as great and quite as distinct as the variations which have been described previously from time to time.

I think it is interesting at this time to call attention to a remarkable similarity between our ideas concerning influenza and our ideas concerning the only animal disease which can be compared with it. I refer to hog cholera. In 1888, Dr. Smith isolated the bacillus from a typical epidemic of the disease, reproduced the disease, and everyone became convinced that the organism was the cause of it. Subsequently, Dr. Welch was able to reproduce the ulcers in the mouth regarded as diagnostic. Gradually, however, some doubt was thrown on this belief. The first definite statement in contradiction was a publication by De Schweinitz, who said that he had been able to reproduce the disease with the serum with all its clinical manifestations, but with no trace of the bacillus. Since that time there have been many epidemics of hog cholera where the bacillus could not be found and yet the disease could be reproduced with a virus. The reactions are very clear and distinct. At the same time in the natural disease there are many cases of hog cholera in which we do find the bacillus. We have the same thing in influenza. If we hypothecate that there is some other cause for this disease I think the analogy would be almost complete.

Just a word or two calling attention to the public health aspect of influenza. Dr. Howard's point in regard to restrictive measures should be emphasized, for there is no evidence that any of the restrictive measures which were undertaken had any influence in checking the spread of this disease. It is a question whether it is wise to carry out the drastic restrictive measures which were attempted. When one comes, however, to a consideration of a pandemic such as occurred here, then health authorities are certainly justified in carrying out any measures that can be suggested, not because there is evidence that the disease may be thus controlled, but on account of the economic question. From an economic standpoint we are justified in applying restrictive measures, but I fail to see that any such measures have in any way influenced the spread of the disease or have altered it in any particular.

Dr. W. G. MacCallum.—When Dr. Welch returned from Camp Devens he reproached us with bad technique because we did not find the influenza bacillus in all our cases. It is a relief to see Dr. Wolbach's specimens, because they correspond closely in form with those in which we did find the influenza bacillus, but are quite different from those studied at Camp Lee and in this hospital in which we did not find the bacillus.

It seems possible that there are local differences in the bacterial flora in different states, so that Massachusetts may be infected with the influenza bacillus while it is not so in Virginia and other places. Late reports from Chicago and other cities describe the pneumonia as due to the pneumococcus.

In view of the fact that we have always found the influenza bacillus as an occasional invader and now find that it can produce alone a peculiar type of pneumonia, I still believe that there is some other cause of the epidemic disease influenza and that the influenza bacillus, like the streptococcus, staphylococcus and various types of pneumococcus, is merely a secondary invader.

I have been much impressed with the resemblance of influenza to such a disease as measles, because in the previous epidemic measles so affected the respiratory tract as to allow the invasion of various bacteria, including even the influenza bacillus. Now we have the influenza lowering general resistance and perhaps sensitizing the respiratory tract to invasion by any organism which happens to inhabit the throat.

Dr. S. E. Howard.—I think Dr. Bloomfield gave the main points of my findings. The influenza bacillus was never found in the blood. In the sputum it was the predominating organism in about 8 per cent of the cases; it was also found in about 30 per cent of the sputum cultures, but not as the predominating organism. In cultures from the nasopharynx it was frequently present, but only in one case was it the predominating organism in a patient who had influenza. A few control cultures were taken from people who did not have influenza and in one of these the influenza bacillus predominated.

Dr. Wm. T. Howard.—I have been greatly interested in these papers. At the beginning of the epidemic I read all the literature I could on the subject, and I could not see that we had any ground to hope that by restrictive measures we could interfere with the number of cases which would occur in a crowded city. I could see how, perhaps, the number in a community at any one time might be modified, but not that the total number of cases would be influenced at all. Therefore I was opposed to any unusual attempts at restriction, and I would be very glad if Dr. Bloomfield would tell us if the evidence he has points in this direction.

I would like to ask several questions. Can we clinically make a diagnosis with any certainty between lobar pneumonia and bronchopneumonia in the great mass of cases in these influenza epidemics? From the standpoint of statistics this is a matter of great importance. It seems to me very unlikely that such a differential diagnosis can be made correctly in many of these cases. This has been attempted in Baltimore. There the doctors have had more fatal influenza cases with lobar pneumonia than cases with bronchopneumonia as the contributory cause of death.

Another questions is, What is the explanation of the large number of cases of pneumonia independent of influenza during these influenza epidemics—that is, primary pneumonia, apparently not occurring as a complication of influenza? This has occurred in all the severe epidemics that have been accurately studied, and it is well known that the year after such epidemics we get a large increase in deaths from acute diseases of the respiratory tract.

Perhaps it would interest you to know something of the disease as we saw it from the health department. It started here about September 20, apparently on the east side of the city. The first cases we heard of occurred in the private practice of two physicians who were also health officers. The early cases were almost entirely among men working at the government construction camps. These physicians told me at first that the disease was entirely a disease of men; but in a few days they changed their tune. The men who had the disease were mostly married, and in a few days their wives came down with it and shortly afterwards their children, and in many families all the children. The disease spread rapidly at Locust Point, where many men work on ships as stevedores, or on repair work of steamers from Europe. We lost over 3500 people in Baltimore in the month of October by death in connection with this epidemic. There were a great many deaths in which pneumonia was given as the sole cause, and I am anxious to find out whether there have been cases of pneumonia in which the influenza attack has been so mild that it has been overlooked. The death rate from a number of other diseases was also very materially affected. The number of deaths from pulmonary tuberculosis was enormously increased, over 50 per cent; from Bright's disease 25 per cent. There was a remarkable increase in deaths from diarrhea and enteritis in children under two years of age—something over 100 per cent. Deaths from heart disease increased almost 100 per cent. Diphtheria went up markedly, entirely out of proportion to the number of cases usually present. The number of deaths from whooping-cough increased four or five times.

All this, of course, from the standpoint of the public health administrator is very interesting. Here is a calamity—you cannot possibly control it, and it leaves us with a number of unanswered questions.

Dr. L. V. Hamman.—The epidemic we have passed through is now nearly over; only a few cases remain in the hospital. However, judging from what has occurred in other epidemics, we are not yet to congratulate ourself upon the epidemic being over, for fresh outbreaks, more limited it is true, may be expected during the winter. At least we have come upon a breathing space and may pause to look back over our experiences and see what fresh information we have gained about the disease.

Following the great epidemic of 1847-49, masterful clinical pictures of influenza were drawn emphasizing all the important clinical and epidemiological features of the infection. It is an inspiration to turn back to these unexpectedly clear, concise, and accurate descriptions.

Following the next great epidemic in 1889-90, an advance was made furnishing still more precise and detailed descriptions of the clinical symptoms, elaborate pathological studies, particularly of the pulmonary complications and bacteriological investigations. During the period from 1850-90, pathology and bacteriology had become highly developed disciplines, and physicians were prepared to study infectious diseases with exact methods which were unknown at the time of the previous epidemic, when acute clinical observation was the only important method of observation. The result of these studies has given us clear and accurate descriptions of the pathological anatomy and of the bacteriology of the pulmonary complications. Either pneumococci or streptococci were found to be the almost constant cause of the associated bronchopneumonia.

Two years after the epidemic was over, Pfeiffer published his discovery of the influenza bacillus. Dr. Bloomfield has stated that his published data do not carry the conviction that the influenza bacillus is the cause of influenza. I quite agree with him that they do not, but Pfeiffer's claims have been accepted, since no opportunity has come since then to test them out.

After the present epidemic is over, I feel sure that the clinical picture of the disease will be filled in with still greater detail. Perhaps our notions of its place amongst the infectious diseases may change. It certainly has many of the features of the exanthemata and while these features have been pointed out before, their importance has not been emphasized. Also, our knowledge of the pathology of the pulmonary complications will be enriched. However, the one great opportunity of the present epidemic is to settle definitely the relation of the Pfeiffer bacillus to the disease. Returns of investigations are rapidly coming in from all parts of the country. Unfortunately, they are not all in accord; indeed, the greatest discord exists. For the present, I must take my stand entirely upon the work done in this clinic, but on the basis of this work I unhesitatingly proclaim my conviction that the Pfeiffer bacillus is not the specific cause of influenza.

Dr. S. B. Wolbach.—I am perfectly willing to concede a great deal on this question of etiology. Everyone has been kind enough not to mention this evening the fact that Nicolle has already announced the discovery of a filterable virus for influenza. There was an account of it in the last number of the *Journal of the American Medical Association*. Nicolle was able to produce grip-like sensations in man and monkey, with an incubation period of six days, by the injection of filtrates of secretions diluted with salt solution from influenza cases. Before this announcement appeared, Dr. Rosenau and his associates at the Naval Hospital in Chelsea, made similar attempts without success. They excluded the possibility of a filterable virus. A filterable yirus, as you know, has already been reported for common colds. This organism has been cultivated and resembles the globoid bodies of poliomyelitis. I refer now to the work of Foster. The experimental evidence for this organism being the cause of one type of common colds is very good, as Foster reproduced the disease in volunteers with his cultures. It seems possible that Nicolle may have encountered the same virus that Foster found. When I went to Camp Devens one of the first things about the epidemic emphasized by Major Churchill, who was then chief of the medical service, and a prominent pediatrician of Chicago, was the striking similarity of the initial stage of influenza to measles, but here again measles may very well be, I believe is, a disease of the respiratory tract.

JANUARY 29, 1919

1. A Functional Re-education Clinic: Organization and Methods. Dr. W. G. Thompson, New York.

My talk this evening really is not a talk, but an exhibition of lantern slides. Referring to the work in which recently I have been interested in New York, and the clinic which I have organized, the story is briefly this:

A long-time friend, a patient of mine, came to me about a year and a half ago and asked if I would not take over and equip a base hospital, to be placed under the charge of the French Government for its use. For this purpose she put a large sum at my disposal. I was to secure the staff and equip the hospital in this country and act as its agent here. But the difficulty of securing the personnel, because so many of our men had already gone abroad, or wanted to wait and go under the United States Government, caused this project to be abandoned.

I had been reading about the wonderful work being done in England and France since the onset of the war, in the reconstruction and re-education of the mutilated. I was convinced that there was a wide field in this country for such work, and, so far as I could see, there was no institution organized here for that purpose; hence, there seemed to be a fine opportunity to organize an institution for functional re-education.

We talked the matter over and were convinced that such an institution was needed for the re-education of the industrial worker after the immediate wants of the returning soldier and

sailor had been met, and that the institution ought to be continued for the men who had been so unfortunate as to have been maimed or mutilated, possibly on the railway, in the factory, or in a street accident, if you will, but for which at the present time there is very inadequate after-treatment provided.

Take, for instance, a large hospital like Bellevue. A man is brought there badly injured. An amputation is performed, and when the wound is healed the man goes out, recorded as "cured." It is true that the social service workers interest themselves in seeing that such a man is provided with an artificial arm or leg, as the case may be, but training him to use his muscles and nerves to the best advantage is not provided, and this is the work we are doing.

I think you will be surprised at the extent of the literature already published on this subject. Bibliography of 40 pages [passed around], gotten up by The Red Cross Institute for Crippled Soldiers, has been compiled from articles written and published in England, France, and Italy, and before we got into the war, in Germany. This is a very considerable literature to have been developed in this short time. It gives one a little idea of the work that has been done and is now being done on the other side.

[Lantern slides were here shown of reconstruction hospitals in France and England, and Dr. Thompson's Clinic, as well as pictures of the individual workers in these institutions, showing the varied utilization of the new apparatus for armless and legless men. This contrasted with a picture of Captain Cuttle with his iron hook and Peter Stuyvesant with his wooden peg for a leg, to emphasize the strides in modern help for the maimed and mutilated. Pictures were shown of the apparatus for mechanotherapy devised by Major R. Tait McKenzie, M. D., of Philadelphia, now in use in the Clinic for Functional Re-Education, organized by Dr. Thompson, in New York, with some of the apparatus devised by Prof. E. A. Bott, of Toronto, and Major R. Tait McKenzie, of Philadelphia, full explanation of the methods of work being given by Dr. Thompson. Pictures also were shown with descriptions of this clinic and hospital with its complete equipment for hydrotherapy, mechanotherapy, electrotherapy, etc.]

DISCUSSION

Dr. Welch.—Is a survey being made among the employers as to the possibility of these men being put into any trade?

Dr. Thompson.—We are not doing that work. Our work is on the side of functional treatment, and we are trying to keep within that line, but the Red Cross, in the spring of last year, had a fund of $50,000 given for the purpose of establishing an institution which would look after the vocational training and make such a survey. A very extensive survey was also made in Pennsylvania. Too many trades are undesirable, and if you concentrate on teaching eight or ten trades, it is possible that many of the men can shortly be trained to make their own living.

Mrs. Henry M. Thomas.—Is this the local branch of the Red Cross?

Dr. Thompson.—It is part of the national organization to which I refer, under Mr. Douglass C. McMurtrie.

I might say in regard to the organization, that we have, of course, an orthopedic surgeon at the head, and an assistant surgeon, who is on duty all the time to examine new cases, and see that the histories are carefully recorded, etc.

Stenographers record all histories. Instead of trained nurses exclusively having the care of the patients, we have 35 volunteer aids. The social service work is also a most interesting one. In asking the men what work they prefer to do, it has been found that the marines, while undergoing functional treatment, usually select typewriting and Spanish. Because of this, we sent out and got 12 typewriting machines and are giving them typewriting lessons. Our X-ray man speaks Spanish and he is giving instruction in Spanish. The men feel that the great opportunity for trade in the future for this country will be with South America, and they feel that knowledge of Spanish will be most useful in what they look to be a great field. We, of course, also have a number of entertainments for the men.

Dr. Welch.—I think this is one of the great outcomes of the war that one likes to think of—the compensations that are discovered in the great development work of so-called re-education and vocational training. Not that it was altogether unknown before, but it has received a tremendous impetus and the public has come to have some sort of an understanding of what is being done. I recall when it was first talked of that Dr. Winford Smith said: "That is exactly what the properly organized ordinary civic hospital should feel its function to do. For the surgeon to send out a maimed and mutilated man is not satisfactory—that man first should be re-educated and taught." This is a broadening of the idea of what should be the function of a hospital to a community, of course, is one of the results of this work.

Dr. Thompson has identified his name with this line of work and he has done a splendid service.

I was not fortunate enough to hear Sir Arthur Pearson when he was here the other night and spoke to our medical society, although no doubt many of you here to-night did have that pleasure, but I did hear him at an after-dinner talk in Washington and he was tremendously thrilling and stimulating. He brought out one point particularly—that the gain is re-education, which is also bringing a broadening of personality of the individual. These blinded, re-educated persons are cleverer and have more brains than ever before. As the Secretary of War expressed it: "They are removed from the tyranny of one faculty. We do not know it, but we are under the tyranny of one faculty, our eyesight. A man who has previously been engaged in some other occupation requiring some kind of intellect, is so much the keener, so much cleverer than he was before, that his ordinary capacity is much greater than before." He gave one or more instances. It was a most inspiring and thrilling talk of the outcome of the war, and was a great contribution to what the duties and obligations of the country are to our disabled soldiers and sailors and also to the

industrial workers. It is an obligation of the government to restore the men it has called from civil life, to do its great work for civilization, to other occupations in which their lives will be in as nearly good condition as when it took them. This is a plain obligation. I do not know, and we cannot tell except from experience, how successful we are going to be. I confess I am somewhat apprehensive about whether we are going to be as successful in this line of work as they have been in England and France. I am frank to say that I do not think this responsibility should be divided among the three agencies—an entirely new outside civilian agency, such as Dr. Thompson referred to, the War Risk and Insurance Division and the Division of Physical Reconstruction of the United States. With these provisions, unless a man follows the lines they are obliged to follow, I do not see that it is any protection, or at least it is a very limited protection. The fact that there is no centralization, that a man passes from one agency to another, from the medical to the civilian, makes it for the moment a very unsatisfactory instrument. It is improving very much under our surgeon-general, who is a very able man, and I think it is getting better all the time.

We are very much indebted to Dr. Thompson. I am certain that we have a great deal to learn here at Johns Hopkins Hospital. I am sure we are not beginning to do our duty in this line, but at least we are awakening to what is our duty—to see that a patient is not sent out handicapped and disabled as a result of wounds.

Dr. Milton J. Rosenau, Professor of Preventive Medicine and Hygiene, Harvard Medical School.—Dr. Welch has asked me to tell what we are doing at Harvard in industrial hygiene. I do not know what excuse there should be for me to speak on the movement of industrial hygiene at Harvard, unless it rubs elbows closely with the subject that has just been presented so illuminatingly by Dr. Gilman Thompson. Industrial hygiene is a very important chapter in preventive medicine, and I have regretted very much for years that we have had so little active work along this line in our country. Through the inspiration and zeal of Dr. Frederick C. Shattuck, Emeritus Professor of Medicine, Harvard Medical School, quite a large sum of money—it seems large to us—was gathered for a number of years for the purpose of research and teaching in "industrial health." The enterprise thus hatched was put in charge of a Committee on Industrial Hygiene, including Dr. F. C. Shattuck, Dr. D. L. Edsall, Dr. Reid Hunt, Dr. M. J. Rosenau, and Dr. C. K. Drinker. I think the only reason I was made a member of the committee was to be sure that the new movement of industrial hygiene would co-operate with our school of public health. It was plain to our committee that no one department could cover such a wide field as industrial hygiene. Industrial hygiene at Harvard, therefore, is not a department; it is not a division; it is not a separate school: it is just industrial hygiene, but doubtless it will soon find a nest.

Now, we proceeded on three lines: one, research; two, teaching; three, publication. I will take a few minutes to outline a few important points about each one of these three.

(1) *Research.*—We have decided to concentrate as far as possible on a few lines, rather than scatter our efforts. One of the problems of industry at present being studied is manganese poisoning, an industrial poisoning about which comparatively little is known and towards which a certain amount of progress has already been attained. Another problem soon to be studied is the sanitation of mercantile establishments. By "mercantile establishments" we mean the large department stores, and until you look into this question with more or less thoroughness one has no conception of the inadequate handling of the problem. A special fund has been provided for this study, which interlocks with sociology, economics, sanitation, and preventive medicine. These examples are cited to give you an idea of the kind of research we are trying to do.

We have made a resolution not to butter our bread too thin. In other words, it is the intention of the committee on Industrial Hygiene to concentrate in certain directions, and we have selected first to develop industrial physiology; industrial chemistry will probably come next.

(2) *Teaching.*—This is on three different levels. Our chief object is to train physicians to take charge of the personnel in large industrial establishments. Those in charge of these stations now have learned their job through experience, and some have made good, although this work is mostly done in an unsatisfactory way. Courses are given in industrial physiology, industrial pathology, toxicology, preventive medicine, and the legal side of industrial medicine. Use is made of the industrial clinic under the charge of Dr. D. L. Edsall, at the Massachusetts General Hospital. The curriculum provides for intensive training, which runs about four months in the theoretical sciences, which are fundamental. Following this, we provide practical work in what we call our industrial clinics. In other words, arrangements have been made with industrial physicians in several large establishments in and around Boston to take our students. The students go to these establishments not simply as on-lookers, but are required actually to assist in the work for a certain period of time under the direct supervision of the physician in charge. In this way, our students spend some weeks with Dr. F. E. Schubmehl, of the General Electric Company; Dr. W. Irving Clark, Jr., of the Norton Grinding Works; and Dr. W. F. Dolan, of the Fall River Ship Yards. We have also made arrangements with other establishments, so that all our students may get the industrial point of view and learn the problems of industry before taking charge of establishments on their own responsibility.

For those who desire to carry out original research, ample opportunity is afforded in the various departments of the Harvard Medical School, and such work may be offered for either the degree of Doctor of Philosophy or the degree of Doctor of Public Health.

On the third level are those who want to be inspectors or industrial aides. I am inclined to develop this a little in detail for the reason that it is in line with Dr. Gilman Thompson's work in the New York Clinic for Functional Re-Education of Soldiers, Sailors, and Civilians. It seems that most of

the men and women who are at present doing physico-therapy have obtained this training from dancing masters or in institutions for physical training of the type of Muldoon's. In this work, we co-operate with Dr. Lovett and the children's hospital work. A school has been started to train women to do the things which the volunteer workers are now doing along the lines of physico-therapy and reconstruction. For the present, this work is fostered by the War Department for its injured soldiers, but we are fully alive to the fact that reconstruction for the military establishment is a comparatively small problem and will not last very long; that is, it is small and temporary as compared with the reconstruction work required for the industrial work. The number mutilated in railroads, mines, and industry have not been given the attention that the subject warrants, and which has been so clearly set forth by Dr. Gilman Thompson this evening.

(3) *Publication.*—I am happy to be able to report that we have started a *Journal of Industrial Hygiene*. The first issue will appear in May, and will come out every month. It will contain original articles, reviews, and literature on the subject, covering a wide field. The *Journal of Industrial Hygiene* will be edited by Dr. D. L. Edsall, with a staff of associate editors, including Dr. W. I. Clark, Jr., Dr. Alice Hamilton, Dr. Y. Henderson, Dr. H. E. Mock, Dr. J. W. Schereschewsky, Dr. C.-E. A. Winslow, and Dr. W. H. Howell; and managing editors, Dr. K. R. Drinker and Dr. C. K. Drinker.

We naturally expect that a journal of industrial hygiene will help stimulate work in industrial hygiene, not only in this country, but abroad, for it will be international. I think you will agree with me that it will doubtless serve a useful purpose.

DISCUSSION

Dr. Thompson.—How are you going to arrange your courses as to those who already have positions as industrial physicians and those who want to be trained for this work?

Dr. Rosenau.—In addition to the regular courses, we have provided for special students. To those who take full course we offer either a certificate or a degree; special students who are qualified may take particular work to fit them better for their responsibilities.

Dr. Thompson.—Then it is like a post-graduate course?

Dr. Rosenau.—In part.

Malaria in the Federated Malay States. A Correction. Dr. W. G. MacCallum.

In the March, 1918, number of this Bulletin, in discussing Col. Whitmore's paper, I evidently made a misstatement with regard to the death-rate for malaria in the Federated Malay States. My attention has been called to this by the Executive Engineer of Public Works in Kuala Lumpur and by Dr. Stanton in letters and I am anxious to correct it. I spoke from memory of a conversation with Mr. Evans, the engineer, who showed me the system of drains constructed for the purpose of combating malaria, and intended to convey the impression which I had received, that among the coolies actually engaged in these excavations, that is, in the most dangerous exposure, the mortality reached those extraordinary figures. But that even in this particular case this estimate was wrong appears from Mr. Evans' letter, in which he states that "the worst individual estates I can call to mind have not exceeded a general death-rate of 600 per mille in any one year." His report for the year 1916 gives the following figures which bear upon the actual general and malarial death-rates:

Year	Population	No. of deaths	Death-rate
1911	1,045,947	40,914	39.11
1912	1,081,799	40,961	37.8
1913	1,117,625	38,000	34.0
1914	1,136,500	39,000	34.31
1915	1,172,336	33,899	28.92
1916	1,208,177	36,981	30.6

Malaria fever accounted for 17,627 deaths or 47.66 per cent of the total deaths. The death-rate per thousand of the population from malarial fever was 14.58 as compared with 12.97 in the previous year.

The total deaths and mortality rate from malarial fever for the past six years are set out below:

Year	Deaths	Per cent	Per mille
1911	17,440	45.02	17.47
1912	17,870	44.02	16.52
1913	16,414	43.19	14.69
1914	13,634	34.95	11.99
1915	15,208	44.0	12.97
1916	17,627	47.66	14.58

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